Study Title: Randomised Controlled Trial of Self-management of Postnatal Antihypertensive Treatment

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Please declare any/no potential conflicts of interest.

Richard McManus and Lionel Tarassenko have previously developed digital interventions for hypertension monitoring including in pregnancy which have been licenced by the University of Oxford to Omron and Sensyne.

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1. KEY CONTACTS

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2. LAY SUMMARY

High blood pressure (BP) (hypertension) during and following pregnancy affects around 80,000 women* each year in the UK, and can lead to very serious problems such as pre-eclampsia or stroke. In the longer term, women who had high BP in pregnancy have an increased risk of heart attack and stroke, and this seems to be linked to their blood pressure in the early weeks following birth.

After birth, women's BP can remain elevated, but in most cases it returns to normal over 2–12 weeks. During this period, blood pressure medication needs to be adjusted to achieve the correct control. Our previous research suggests that better BP control during this period is associated with improved long-term health outcomes. This trial aims to test whether women with high BP , can achieve lower blood pressure than is usual in the weeks and months following birth, through self-monitoring and adjusting their own medication.

Women recruited to the study will be randomly assigned to one of two groups: either monitoring their own blood pressure and using this to manage their blood pressure medication, or receiving the standard care that they would otherwise have. Participants allocated to 'usual care' will have their BP monitored and medication adjusted by their obstetrician, GP and midwife as normal. Participants allocated to the 'self-management' group will use a home BP monitor daily following discharge from hospital after birth until their blood pressure has settled, and then once a week. They will be provided with an individualised schedule (via a specially designed app) for gradually adjusting their medication(s) in line with their BP readings, overseen by their obstetrician, GP and midwife.

Women will be followed up for 12 months, and the trial will measure blood pressure as well as their experiences and costs. Results will be widely shared in both professional and lay media.

*Throughout the Protocol, in our references to women, we also encompass birthing people within this context

3. SYNOPSIS

Study Title	Randomised Controlled Trial of Self-management of Postnatal Antihypertensive Treatment
Internal ref. no. / short title	SNAP2
Study registration	ISRCTN: 11042045
Sponsor	University of Oxford Research Governance, Ethics and Assurance, Boundary Brook House, Churchill Drive, Headington, Oxford, OX3 7GB
Funder	NIHR Programme Grant for Applied Health Research
Study Design	Multicentre randomised controlled trial

Study Participants	Women in the postnatal period, requiring antihypertensive treatment		
Sample Size	At least 532 women with gestational hypertension resulting in a total, including with women with chronic hypertension, of approximately 690		
Planned Study Period	April 2024 - January 2027		
Planned Recruitment period	April 2024 - November 2025		
	Objectives	Outcome Measures	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary	To evaluate whether self-management of postnatal hypertension leads to lower diastolic blood pressure	Mean daytime ambulatory diastolic blood pressure	22-39 weeks
Secondary	To evaluate whether self-management of postnatal hypertension leads to lower systolic blood pressure	Mean daytime ambulatory systolic blood pressure	22-39 weeks
	To assess nocturnal ambulatory clinic blood pressure	Mean 24 hour and nocturnal ambulatory blood pressure	22-39 weeks
	To assess clinic or at home measured systolic and diastolic blood pressure	Systolic and diastolic blood pressure at follow up (mean of 2nd/3rd readings and mean of 2nd – 6th readings) measured in clinic or at home.	Baseline[1] 6 weeks 12 weeks 22-39 weeks 48-60 weeks
	To assess participant reported health-related quality of life and anxiety associated with self-management of blood pressure	Maternal health-related quality of life (EQ-5D-5L health questionnaire results)	Baseline 6 weeks 12 weeks 22-39 weeks 48-60 weeks

[1] Baseline readings taken from maternity notes)

	in the postpartum period.		
	To assess anxiety	Short form anxiety inventory questionnaire	Baseline 12 weeks 48-60 weeks
	To assess medication adherence	Presence of urinary antihypertensive metabolites MARS questionnaire	6 weeks Baseline 6 weeks
	To assess if BP self-management postpartum can reduce postnatal readmissions to hospital associated with hypertension	All cause admissions Pregnancy hypertension admissions Cardiovascular events	Records review at end of trial period
	To assess the impact of self-management of blood pressure during the post-partum period on healthcare resource use and costs	Healthcare resource use and cost analysis of key cost drivers between study arms	Participant resource use data collection at: Baseline 12 weeks 22-39 weeks 48-60 weeks
	Assessment of joint impact of self-management of blood pressure during the post-partum period on healthcare costs and health outcomes	Cost-consequence analysis presenting costs and key outcomes in a disaggregated manner	Over trial period
		Long term modelled cost-utility analysis using quality-adjusted life years (QALYs)	Modelled lifetime horizon Sensitivity analysis to judge time to benefit/harm
Long term follow-up	Determine the difference in the percentage of participants	Blood pressure Cardiovascular events	10 years post-randomisation follow up (subject to further funding)

	developing hypertension and/or experiencing a cardiovascular adverse event between the randomised groups at 10 year follow-up		
Qualitative Process evaluation	To understand how postnatal self-management of blood pressure is enacted and integrated into women's lives and clinical pathways	In depth semi-structured interviews focused on acceptability and experience including an optional photovoice activity with a sample of participating women and those who decline to take part, and in depth semi-structured interviews with healthcare professionals involved in delivering the intervention, to understand: • Experiences of women and healthcare professionals of their involvement in the trial • the reason(s) why some women chose not to participate in the trial • Views of women and healthcare professionals around the subject of self-monitoring and self-management of blood pressure, and the interface between secondary and primary care • Views of healthcare professionals on the integration and implementation of new technologies and	Ongoing throughout trial period

		complex interventions in health care	
Intervention(s)	The intervention will consist of BP self-monitoring using a validated monitor and titration of antihypertensive therapy guided by a specially developed digital intervention (a 'smartphone' app). This will be overseen, with any change approved by their own health care professionals who review the uploaded readings and respond to tele-monitored abnormal readings in a timely fashion. All intervention participants will in addition receive usual NHS care.		
Comparator	The control arm will be managed according to usual NHS care with assessment by their own health care professionals and adjustment of medications as required.		

4. ABBREVIATIONS

ABPM	Ambulatory Blood Pressure Monitoring
AE	Adverse event
BNF	British National Formulary
BP	Blood Pressure
CI	Chief Investigator
CRF	Case Report Form
DAU	Day Assessment Unit
DMC	Data Monitoring Committee
DMP	Data Monitoring Plan
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
HELLP/ELLP	Hemolysis, Elevated Liver enzymes and Low Platelets
HRA	Health Research Authority
ICF	Informed Consent Form
IPD	Individual Personalised Data
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
LC-MS/MS	Liquid Chromatography with tandem mass spectrometry

MAR	Missing At Random
MAU	Medical Assessment Unit
NHS	National Health Service
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
PC-CTU	Primary Care Clinical Trials Unit
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QALYs	Quality-adjusted life years
R&D	NHS Trust R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGEA	Research Governance, Ethics & Assurance
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

4.2 DEFINITIONS

Hypertension	Sustained high blood pressure measured by a professional equal to or greater than 140mmHg or 90mmHg, or a clinical label of hypertension accompanied by antihypertensive treatment.
Pre-eclampsia	New hypertension presenting after 20 weeks with one or more new-onset features, including significant proteinuria or maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological complications or haematological complications (NICE, 2019)
Gestational Hypertension	Hypertension presenting in pregnancy at 20 weeks or later without pre-eclampsia
Chronic or Essential Hypertension	Hypertension predating pregnancy or presenting before 20 weeks without pre-eclampsia
Raised blood pressure	Blood pressure measured by a professional equal to or greater than 140mmHg or 90 mmHg.

5. BACKGROUND AND RATIONALE

5.1. What is the problem to be addressed?

This trial is part of a research programme that will co-develop and evaluate a self-management intervention to better control blood pressure (BP) for women in the postnatal period following hypertensive pregnancy with the aim of reducing both their short and long-term cardiovascular risk. Hypertensive disorders of pregnancy affect around 10% of women (over 80,000 women per year in the UK), affecting millions worldwide (Yoder SR, 2009) (Ananth CV, 2013) (Bateman BT, 2012) (NICE, 2010). Pregnancy hypertension is important antenatally due to its impact on maternal and neonatal morbidity and mortality, particularly related to the risks of stroke and pre-eclampsia. It often persists postnatally when women are coping with many competing priorities and may have rapid, often unpredictable BP changes (Berks D, 2009). Furthermore perhaps a third of serious morbidity and mortality associated with pregnancy hypertension happens after birth.

Care of women with hypertension following maternity discharge is often haphazard (Cairns AE, 2016) with little evidence to guide best practice and often sub-optimal support due to the transition from the maternity setting to primary care (Magee L, 2013) (Davies, 2015). Post-natal care and research is neglected relative to pregnancy and birth care and seems to have suffered even further with the impact of Covid-19 on services. It is not widely understood that the health risks from pregnancy hypertension are enduring: although BP often initially returns to normal over weeks or months, women remain at approximately double subsequent risk of hypertension and cardiovascular disease for at least the next twenty years (Podymow T, 2010), (Leon LJ, 2019). Previous work by Prof McManus' group has shown that self-management of hypertension, where people self-monitor BP and then follow pre-planned medication titration algorithms is effective in general primary care populations (mean age 60s-70s) leading to better control of BP (McManus RJ, 2010), (McManus RJ, 2014). However, the intervention proposed here is different as most women (mean age 30s) require down (rather than up) titration and the postnatal timescale for intervention is short, but with a need for timely responses. Furthermore, the interface issues between primary and secondary care and affected women are unique in the postnatal period (Bick D, 2020).

The short-term effects on BP following pregnancy hypertension appear to be linked to much longer-term influence on women's cardiovascular health, hence any intervention that can mitigate these may have substantial impact (Lazdam M, 2012), (Boardman H, 2020). Blood pressure six weeks following a hypertensive pregnancy is correlated with future risk and changes in cardiac structure and geometry are evident in midlife following pregnancy hypertension (Lazdam M, 2012), (Boardman H, 2020). The results from the SNAP-HT feasibility work (detailed below in the summary of findings from previous studies) provide hope that such changes may be reversible with timely intervention (Cairns AE, 2018), (Kitt JA, 2021).

5.2. Summary of findings from previous studies

Outside of pregnancy, in both essential hypertension and people at higher cardiovascular risk, BP self-monitoring with self-titration leads to better BP control, with economic models reporting that self-management is cost-effective and even cost saving in those at the highest risk (Penaloza-Ramos MC, 2016), (Kaambwa B, 2014).

A systematic review found no evidence to guide postnatal treatment of BP other than a few small trials in the immediate postnatal period (mostly in the first 48 hours) (Cairns AE, 2017). Since then the PICK-UP feasibility trial has suggested that ACE inhibitors may improve echocardiographic measures of diastolic function and left ventricular remodelling, but further work will be needed before this intervention is adopted more widely (Ormesher L, 2020). Arguably postnatal treatment should be equivalent to the situation outside of pregnancy; however, women will have been stabilised prior to birth on very different medications (such as labetalol), are likely to be breast-feeding (affecting drug choice) and are at risk of iatrogenic hypotension if treatment is not adjusted much quicker than would be usual in essential hypertension (Webster K, 2019). Furthermore, the key decisions tend to be about medication reduction not medication increase emphasising the difference from management plans outside of pregnancy (Boffa RJ, 2019).

Our published feasibility work in the Self-management for Post Natal Hypertension trial (SNAP-HT, NIHR funded, n=91) showed that in women from five hospital sites within one region who self-titrated their own antihypertensive medication (using daily self-monitoring with automated medication reduction facilitated by a smartphone-based app), there were short-term (6 weeks), medium-term (6 months) and long-term (3-4 years) reductions in BP (Ananth CV, 2013), (Cairns AE, 2017). Of eligible women, 66% agreed to participate.

Women self-monitored daily with 85% adherence, 94% reporting accuracy and 90% follow-up. Although the trial was not powered to show BP differences, both systolic and diastolic BP were lower in those self-managing at six weeks: adjusted mean difference 5.2/5.8mmHg in systolic/diastolic BP. Importantly, even when women stopped taking their antihypertensive medication, diastolic BP remained lower; at six months there was an adjusted difference of -4.5mmHg (95%CI -8.1, -0.8), (with >95% off medications). There were no serious adverse events associated with self-management.

Trial participants (n=61) were followed up recently (3-4 years post-trial) using 24-hour BP monitoring; those who had self-managed were found to have ongoing mean daytime ambulatory diastolic BP reduction of −5.3mmHg (−8.6 to −2.0); P=0.002 compared to those receiving usual care (Ananth CV, 2013).

5.3 What is the study intervention?

The intervention involves BP self-monitoring using a widely available (over the counter) validated blood pressure monitor and use of a digital intervention My Blood Pressure Care (an app – academically developed for the purpose of the trial) to transmit blood pressure readings (Cairns AE, 2018). This

facilitates real-time automated feedback of blood pressure including motivating reminders and providing information to clinicians to inform titration of antihypertensive therapy via a web-based dashboard and email alerts. The intervention will be designed to be easy to use and relevant for women from all backgrounds of social strata and ethnicity. Medication down-titration will be clinician led and follow usual practice for reducing doses gradually, one medication at a time as in our pilot trial (Cairns AE, 2016) and will follow national guideline thresholds for down-titration (Webster K, 2019).

All data entered into the SNAP2 digital intervention will be stored on NHS servers, behind NHS firewalls, owned by Oxford University Hospitals (OUH) IM&T, and physically located on the John Radcliffe Hospital in Oxford. The servers have been leased to the Biomedical Signal Processing and Machine Learning group (BSP-ML) from the Institute of Biomedical Engineering (IBME), University of Oxford, as part of ongoing collaborations for the past 10 years.

At registration, participants will be assigned a study number (study IDs) and the system will automatically generate a random unique identifier. All data stored in the system database is based on the randomly generated unique identifier. The linkage table between the Study IDs and the randomly generated unique identifiers is stored in a single location, under an encrypted and password protected database, and will only be shared with the principal investigator at the end of the study

5.4. Potential Risks

During the trial, participants will continue to receive usual care regardless of randomisation group. As such we anticipate that the potential risks are low. Particular issues include a participant in the self-management group obtaining an excessively high or low BP reading and the possibility of increased anxiety due to the study. We aim to minimise any potential risks due to poor blood pressure control by ensuring women have clear advice regarding when to seek urgent medical help. The participant guideline/booklet will give clear advice to women to contact their healthcare professionals (e.g. obstetrician, midwife, general practitioner (GP) dependent on timing) in the case of maintained high or low readings. This will be reinforced by messages from the app when they submit a blood pressure reading that is outside the target range.

The first 14 days postpartum

Women in the self management group will also receive usual blood pressure monitoring and management by their community midwife and GP following their discharge from hospital. For women with high blood pressure, in the first 14 days after birth, NICE recommends that BP is monitored on at least alternate days (NICE, 2023). Therefore, in the first 2 weeks following discharge, reminders for self-monitoring are more frequent but usual care will continue fulfilling NICE requirements.

From 14 days postpartum

From 14 days after delivery until antihypertensive treatment is discontinued, women will be encouraged with reminders via the app to upload their readings. If a participant is unable to engage, it will be deemed that the woman has discontinued from the intervention but follow-up will continue unless the participant wishes to definitively withdraw.

5.5 Potential Benefits

Potential benefits for individuals taking part include better information about their BP and possible better control of BP. Current national and international guidance for the post-partum care of pregnancy hypertension lacks robust, high-quality evidence to guide practice and we hope to provide data that helps improve this aspect of care.

5.6. Rationale

We hypothesise that the intervention works by improving BP control at a time of significant cardiovascular remodelling following pregnancy hypertension (Ormesher L, 2020) (Kitt, 2023). Through this process, short-term postpartum BP optimisation may reverse some of the previously deleterious cardiovascular effects of pregnancy hypertension, providing one of the first interventions to do so. The aim of this trial is to test the clinical and cost-effectiveness of an intervention to support self-monitoring of blood pressure and titration of antihypertensive medication following a hypertensive pregnancy with the aim of improving long-term BP control and therefore reduce adverse cardiovascular outcomes and the associated costs to the NHS.

6. OBJECTIVES AND OUTCOME MEASURES

	Objectives	Outcome Measures	"**Timepoint(s) of evaluation of this outcome measure (if applicable**
Primary	To evaluate whether self-management of postnatal hypertension leads to lower diastolic blood pressure	Mean daytime ambulatory diastolic blood pressure	22-39 weeks
Secondary	To evaluate whether self-management of postnatal hypertension leads to lower systolic blood pressure	Mean daytime ambulatory systolic blood pressure	22-39 weeks
	To assess nocturnal ambulatory clinic blood pressure	Mean 24 hour and nocturnal ambulatory blood pressure	22-39 weeks

	To assess clinic or at home measured systolic and diastolic blood pressure	Systolic and diastolic blood pressure at follow up (mean of 2nd/3rd readings and mean of 2nd – 6th readings) measured in clinic or at home	Baseline [2] 6 weeks 12 weeks 22-39 weeks 48-60 weeks
	To assess participant reported health-related quality of life and anxiety associated with self-management of blood pressure in the postpartum period.	Maternal health-related quality of life (EQ-5D-5L health questionnaire results)	Baseline 6 weeks 12 weeks 22-39 weeks 48-60 weeks
	To assess anxiety	Short form anxiety inventory questionnaire	Baseline 12 weeks 48-60 weeks
	To assess medication adherence	Presence of urinary antihypertensive metabolites MARS questionnaire	6 weeks Baseline 6 weeks
	To assess if BP self-management postpartum can reduce postnatal readmissions to hospital associated with hypertension	All cause admissions Pregnancy hypertension admissions Cardiovascular events	Records review at end of trial period
	To assess the impact of self-management of blood pressure during the post-partum period on healthcare resource use and costs	Healthcare resource use and cost analysis of key cost drivers between study arms	Participant resource use data collection at: Baseline 12 weeks 22-39 weeks 48-60 weeks
	Assessment of joint impact of self-management of	Cost-consequence analysis presenting costs and key	Over trial period

[2] (Baseline readings taken from maternity notes)

	blood pressure during the post-partum period on healthcare costs and health outcomes	outcomes in a disaggregated manner	
		Long term modelled cost-utility analysis using quality-adjusted life years (QALYs)	Modelled lifetime horizon Sensitivity analysis to judge time to benefit/harm
Long term follow-up	Determine the difference in the percentage of participants developing hypertension and/or experiencing a cardiovascular adverse event between the randomised groups at 10 year follow-up	Blood pressure Cardiovascular events	10 years post-randomisation follow up (subject to further funding)
Qualitative Process evaluation	To understand how postnatal self-management of blood pressure is enacted and integrated into women's lives and clinical pathways	In depth semi-structured interviews focused on acceptability and experience including an optional photovoice activity with a sample of participating women and in depth semi-structured interviews with healthcare professionals (HCPs) involved in delivering the intervention, to understand: • Experiences of women and HCPs of their involvement in the trial • The reason(s) why some women chose not to participate in the trial • Views of women and HCPs around the subject of self-monitoring and self-management of blood	Ongoing throughout trial period

		pressure, and the interface between secondary and primary care • Views of HCPs on the integration and implementation of new technologies and complex interventions in health care	

7. STUDY DESIGN

This study is a prospective, multi-centre unblinded randomised controlled trial with internal pilot and independently measured outcome. The work is part of a larger programme of work investigating optimisation of the management of blood pressure following hypertensive pregnancy. Recruitment will be through around 25-30 UK antenatal care centres, predominantly in secondary care, supported by community organisations or maternity support workers/health navigators.

Women with pregnancy hypertension (including chronic hypertension, 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 will be invited to participate if they have had a hypertensive pregnancy and still require or seem likely to require antihypertensive medication at randomisation. Potentially eligible women will be approached before or soon after delivery. If they agree to take part, they will be consented and baseline data (including bedside BP) will be collected. Participants will be followed up for 48-60 weeks and follow up measurements/questionnaires will take place at 6 weeks, 12 weeks, 22-39 weeks and 48-60 weeks (remote follow up will be offered if this is possible).

Women randomised to usual care are most likely to have their care overseen initially by their obstetric and community midwife teams. Following transfer to primary care, most women will have their care including anti-hypertensive medication overseen by their GP team.

Women randomised to self-management of blood pressure will have an intervention comprising self-monitoring and transmission of blood pressure measurements using a bespoke app. This is described in section 9.6 below.

All participants will continue to receive usual NHS care including for other medical, mental health or social issues. All participants will be followed up at 6 weeks, 12 weeks, 22-39 weeks and 48-60 weeks post-randomisation for questionnaires and blood pressure measurement. Participants will also be required to wear an ambulatory blood pressure monitor between 22 and 39 weeks post-randomisation for a 24 hour period. If women still require antihypertensive treatment at 6 weeks postpartum they will be offered referral to the specialist hypertension clinic or will follow the patient pathway within their area. To reduce

burden on the women, remote follow-up will be used where possible. To account for this, women in the usual care arm will be provided with the same calibrated BP Monitor to take blood pressure readings. Questionnaires can either be completed over the phone or via a link by email/SMS and will include blood pressure measurements, current medication, breastfeeding/formula feeding, primary healthcare contact, adherence, anxiety and quality of life at follow-up as per the schedule.

Additionally, we will conduct a parallel qualitative sub-study with participants eligible for the trial (including both groups) and their health care professionals.

See Appendix A for the study flow chart.

An internal pilot will take place within 6 months including the first 100 women, to confirm that the trial is feasible as planned and to allow adjustment of procedures if not.

7.1. Qualitative sub-study

The qualitative sub-study will provide important data for the process evaluation which will seek to understand the impact and acceptability of the intervention, and how postnatal self-management is enacted and integrated into women's lives and clinical pathways, with a focus on both women's and health professionals' perspectives (in secondary and primary care). The inclusion of both perspectives is crucial to exploring both the potential for, and the barriers to, implementation. In-depth, semi-structured interviews will be undertaken with a wide sample of participating women and a focus on socio-economic and ethnic diversity and healthcare professionals involved in delivering the intervention. Women who take part in an interview will also have the option of taking part in a photovoice activity. Photovoice is a flexible, participatory method that has been widely used in health research to provide context-rich understanding of people's everyday experiences (Seitz & Orsini, 2022). In the case of this sub-study, the photovoice activity involves participating women taking photographs on their smartphone in response to a prompt provided by the qualitative sub-study researcher. These photograph will be shared with the researcher and used during the interview to aid reflection and discussion about the experience of managing blood pressure in the postnatal period using either the intervention or within usual care.

Women who meet the inclusion criteria but who decline to participate will also be invited to interview. To support health equity (see section 9.11) community based (peer) researchers may be used in some sites, via community organisations, to support recruitment to the trial and the qualitative studies.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Women in the postnatal period with all types of pregnancy hypertension, requiring anti-hypertensive treatment. Information will be available at antenatal clinics. Identification will be antenatally or postnatally up to 7 days and randomisation within 7 days of child birth.

8.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- People who have given birth within the last 7 days
- Aged 18 years or above.
- Participant with pregnancy hypertension including: **chronic/essential hypertension** (predating current pregnancy or requiring treatment before 20/40), or **gestational hypertension** (new-onset hypertension from 20/40 of index pregnancy) or **pre-eclampsia** (hypertension (GH or with proteinuria or metabolic changes), prior to their discharge from hospital post-delivery.
- Participant still requiring antihypertensive medication at randomisation following delivery.
- Able and willing to comply with trial requirements.
- Willing to allow their primary and secondary healthcare teams, if appropriate, to be notified of participation in the trial.
- Access to a smartphone compatible with the app.

8.3. Exclusion Criteria

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

- Participant does not wish to self monitor/self manage their blood pressure.
- Participant already taking part in another trial that might affect their anti –hypertensive prescription.

8.4. Qualitative sub-study requirements

People eligible to take part in the trial

Randomised participants must satisfy all the approved inclusion and exclusion criteria for, and have been invited to participate in, the trial. Participants who decline participation or discontinue/withdraw from the trial will be invited to take part in the qualitative substudy.

Healthcare professionals

Participants must be part of the clinical team providing postnatal care for individuals with postnatal hypertension and administering the intervention at participating sites and/or system level policy makers (e.g. NHS England) or local managers.

9. PROTOCOL PROCEDURES

9.1. Recruitment

9.1.1. Main trial recruitment

Women undergoing obstetric care at participating hospitals will be approached by research midwives either late in pregnancy or within 1 week post-delivery. Women not eligible at primary discharge but readmitted within one week post-delivery can be recruited if they become eligible within that time, for example by (re)starting medication. It is anticipated that participants will be recruited from around 20-30 hospitals in the UK and recruitment can be in hospital, in clinic or via remote means. In some sites, recruitment may be supported by community organisations or maternity support workers/health navigators.

The study will be advertised through the use of posters in clinical areas, social media and digital channels. Information leaflets/flyers will be available for women at these sites (through the Antenatal Clinics, Antenatal Wards, Postnatal Wards and Day Assessment Units). In some cases, online searches of hospital records may be appropriate, to identify potentially eligible participants. The study will also be promoted by community groups in some sites. Interested women will be provided with a flyer and participant information sheet (PIS), and asked to give verbal consent to share their details with the research midwives so that the research midwives can contact them for consent and screening. These women will be consented and screened by the research team (including clinical research network (CRN) and local PI team) according to the inclusion/ exclusion criteria detailed in 8.1. Where research professionals work within usual clinical care teams (e.g in hybrid or dual roles), women can be approached directly.

Following birth the research team member will review eligible women who wish to participate in the study for a baseline visit; this visit will take place in the hospital or at home/remotely if they have already left hospital within 7 days of delivery. At this stage, there will be formal confirmation of consent via signing (or remote completion) of the consent form and randomisation will take place via the secure web-based randomisation system. This may be supported by community groups or maternity support workers/navigators in some sites.

Women who suffer an adverse perinatal outcome (Neonatal 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 the approach will be considered sensitively. This follows direct advice and input from lay representatives who have experienced such outcomes.

All potential participants will be recorded on a screening log by the research team at the site.

9.1.2 Qualitative sub-study recruitment

Women

A purposive sample of approximately 30-40 participating women from both arms of the study will be invited to take part in up to 3 longitudinal interviews. Upon invitation, they will be asked if they would like to take part in the optional photovoice activity designed to support the interview(s).In addition, we will include a sample of up to eight women who decide not to take part or withdraw but who are willing to be

interviewed. Those who decline will be asked by the research midwives if they consent to being contacted by a researcher. If they agree, the researcher will then contact them and send them a PIS. When providing those interested in the main study if they wish to participate, we will also ask them if they are happy to be contacted for further information regarding the sub-study. We will recruit women from across the study sites and aim for a diverse sample to help understand the real-life implementation issues with self-management postnatally. Purposive sampling will include women from central and peripheral hospital settings, a range of ages, socio-economic and ethnic background, parity, previous history of raised BP in pregnancy or pre-eclampsia.

Healthcare professionals

A purposive sample of 25-30 participating healthcare professionals involved in the trial from across participating sites (including obstetricians, midwives and GPs as well as those involved with policy making eg NHS England and local managers) will be invited to take part in an interview. The trial team will use the delegation logs to identify site team members to be approached by the qualitative research team. Other healthcare professionals involved in using the trial intervention, such as GPs, will also be identified.

For both women and health care professionals, a detailed enrolment log of participants will be kept to monitor diversity indices of participants. 9.2. Screening and Eligibility Assessment

The screening and eligibility assessment will involve looking at the inclusion/exclusion criteria to see which patients are eligible to take part in the study. Once consented the following data will be collected: demographics, including Date of Birth, weight at booking, height (to allow calculation of Body Mass index (BMI), ethnicity, medical history, pregnancy history, medication history, social history and postcode to allow calculation of IMD deprivation score.

We will ask women whether or not they are involved in any other relevant clinical research projects. Involvement in other research projects does not exclude women from this trial unless they are directly involved with a trial that might affect their anti –hypertensive prescription.

Personal data as follows will be collected and stored separately from the clinical database. 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 full postcode
- NHS Number (to allow access to participant's medical records)
- Telephone number (mobile)
- Email address

Details of the following aspects of the diagnosis of pregnancy hypertension and its complications will be taken from the medical records either pre or post natally but before randomisation and recorded:

- Blood pressure (BP) at booking

- Diagnosis of chronic or gestational hypertension
- Separate diagnosis of pre-eclampsia (including proteinuria or other maternal dysfunction)[can follow chronic or gestational or be denovo)
- Multiple pregnancy
- Maternal complications (renal dysfunction, HELLP/ELLP syndrome, eclampsia, placental abruption)
- Fetal Death

Details of postnatal hypertension

- Date of delivery and estimated date of delivery (to calculate gestation at delivery)
- Baseline postnatal anti-hypertensive drugs used
- Baseline blood pressure: last 3 postnatal readings within 24 hours of randomisation

Participants will be asked to complete the EQ-5D-5L health-related quality of life questionnaire and the Short Form Anxiety Inventory Questionnaire at this visit.

9.3. 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. Informed consent can also be taken remotely. The researcher taking remote consent must personally sign and date the remote consent form. The initial consent and screening process will take place flexibly before or after birth if before there will be a formal confirmation of consent at the baseline visit after delivery. Study procedures will be re-discussed, and a second copy of the PIS will be provided if necessary. Confirmation of consent will be verbal but will be documented in the participant's maternity records (if still an inpatient or seen in clinic) and the baseline CRF. If women are approached for the first time postnatally, then only one consent will be recorded and there will be no requirement for reconfirmation of consent.

Written versions of the Participant Information and Informed Consent forms 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, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will have time between first approach and randomisation 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 or informed eConsent 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 and named on the delegation log. A

copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site in the Investigator Site File (ISF) and a copy will be placed in the participant's medical notes. Where a woman is approached postnatally and wishes to participate on the same day, and confirms they have had sufficient time to consider all the information required, this will be facilitated (in line with similar pregnancy and postnatal studies where women's wishes are respected in this matter). Participants will be asked if they are happy to consent to being contacted for future research.

The participant's GP will be informed in writing (usually electronically) of the participant's involvement in the study.

9.3.1 Qualitative sub-study

As for the trial above, all participants will be provided with the relevant Participant Information Sheet and asked to read this and the associated Informed Consent form (the researcher may read the consent form in full if requested by the participant). The Participant Information Sheet will detail no less than the exact nature of the study, what it will involve for the participant and any risks involved in taking part. It will be clearly stated that the participant is free to decline participation or withdraw from the study at any time without any impact on their care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. The participant will be allowed as much time as wished to consider the information, and given the opportunity to question the researcher to decide whether they will participate in the study.

Written Informed Consent will be obtained by means of participant-dated signature and dated signature of the person who presented and obtained the Informed Consent. We will offer the facility to be interviewed remotely. Remote Informed Consent will be obtained by means of the researcher reading the Informed Remote Consent form to the participant, and on confirmation of each statement, the researcher will initial the consent form on the participant's behalf, and add a dated signature.
A copy of the signed consent form will be given (or sent by University of Oxford approved secure file transfer) to participants for their records. The original signed form will be retained at the University of Oxford.

9.4. Baseline Assessment

The baseline visit will take place as soon as is practical (within 7 days) in hospital after delivery or remotely/at home for women who have left hospital already and will last approximately 45 minutes. For eligible participants who have already consented before the baseline assessment (e.g. if they have been in hospital for a few days and consented before birth), consent will be re-checked to ensure that participants are still happy to continue on the trial, and this will be documented in the participant's maternity notes and on the study CRF. For those not previously consented, the consent process described above will take place before any further activity. Inclusive recruitment procedures will be used.

Any data not already collected as per eligibility screening in 9.2 above will be collected.

Baseline BP will be collected the last 3 postnatal BP readings within 24 hours of randomisation (up to 3 if less than 3 available in records)

We will measure (or ask for self-measurement of) a participant's left upper arm (or right arm if left arm cannot be used for blood pressure monitoring) in order to guide choice of blood pressure cuff size.

It is at this visit that participants will be randomised. If they are randomised to the intervention arm, they will be provided with a blood pressure self-monitor, and taught to use it. For participants in the usual care arm, they will be given a bag to put their monitor in that indicates it should only be used for taking readings at follow up time points (if follow ups are remote). Prior to discharge from hospital, participants in the intervention group will receive the intervention as per section 9.6 below.

9.5. Blinding and code-breaking

Randomisation will be concealed and the intervention unblinded by design. Due to the nature of the intervention it will not be possible to blind participants, the recruiting clinician or data management staff within the clinical trials unit to the group allocation. The primary outcome is collected via an objective automated method (ambulatory monitoring) and the analyst will be blinded to intervention group, thus reducing potential bias.

9.6. Description of study intervention(s), comparators and study procedures (clinical)

9.6.1 Description of study intervention: Self –management of blood pressure

Women randomised to self-management of blood pressure will have an individualised medication adjustment schedule (based on NICE guidance for medication adjustment postpartum) (NICE, 2019), (Webster K, 2019). They will be provided with, and taught how to use, a validated home blood pressure monitor, and perform daily blood pressure readings until their blood pressure has settled on treatment or they have discontinued treatment. Readings will transmitted to their health professionals (obstetricians for first 2 weeks then GP) via a bespoke app (My Blood Pressure Care) (see 5.3 above.

The blood pressure monitor used will be Microlife WatchBP® Home as these have been validated for use in pregnancy and pre-eclampsia. Women will be provided with written instructions regarding use of the monitor. When antihypertensive treatment is discontinued or blood pressure is stable on treatment (in each case for a 7 day period), we will ask them to continue weekly blood pressure measurements until the primary outcome measurement at six months. Should blood pressure increase again during the weekly measurement period, the clinician will advise a change back to daily measurement via the app. Clinicians will have access to the self-monitoring BP data in order to advise on medication titration. Women and clinicians will both receive prompts for action in the event of raised or low blood pressure readings.

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 to their usual care team through the use of a smart phone app. 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 via the app based on:

- Current treatment (which drugs, what doses)
- NICE guidance for management of hypertension in pregnancy (NICE, 2019) suggests the following categories
    - If < 130/80 mmHg reduce / stop treatment
    - If < 140/90 mmHg consider reducing / stopping treatment
    - If ≥ 150/100 mmHg increase / start treatment
    - If ≥ 160/110 mmHg requires hospital review

The individualised medication adjustment schedules for each participant will be created by the participant's usual care team in conjunction with the research team.

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

Participants in the intervention arm will be advised to attend their local maternity unit for urgent review if blood pressure is ≥ 160/110 mmHg or they develop symptoms which may be associated with hypertension (headache, visual disturbance, vomiting or upper abdominal pain). They will also be given instructions on contacting their GP or midwife should their blood pressure be greater than 150/100 mmHg, or less than 100 systolic (or sustained ≥140/90mmHg). Other messaging will relate to the level of blood pressure recorded (see NICE blood pressure categories above) and participants will receive simple advice regarding appropriate actions. If there is no evidence that the participant has made contact with a clinician/GP within a week after a BP reading requiring review was entered, the participant's GP will be sent a letter informing them of this.

In addition, participants randomised to the intervention will receive usual postnatal care provided by a combination of obstetrician, community midwife, health visitor and GP including routine visits and examinations. Participants randomised to the intervention will be provided with a letter to share with their community midwife/ maternity support worker, informing the teams providing postnatal care of the woman's participation in the trial.

9.6.2. Description of comparator(s)

Usual postnatal care provided by a combination of obstetrician, community midwife, health visitor and GP including routine visits and examinations.

9.6.3. Description of study procedure(s)

Refer to appendix B for the schedule of study procedures.

9.7. Randomisation

Participants will be randomised by the site study team after the baseline visit and before primary hospital discharge, using a secure web-based randomisation system provided by the Oxford Primary Care Clinical Trials Unit. If a participant has been discharged from hospital before being randomised the research midwife will contact the participant and carry out remote consent and randomisation over the phone within 7 days of being discharged. The system will allow for the allocation of participants to the two

randomisation groups: usual care or self-management on a 1:1 basis and for this allocation to be stratified according to recruitment site with minimisation for principal diagnosis (chronic hypertension or gestational hypertension/pre-eclampsia), and mean postnatal diastolic blood pressure (last 3 readings in clinical record, <83mmHg vs ≥83mmHg), and number of antihypertensive medications (<2 vs ≥2 medications).

9.8. Follow up

Participants will be followed up for 48-60 weeks after randomisation. Follow up visits in both trial arms will be undertaken at 6 (+/-3) weeks, 12 (+/-4) weeks, 22-39 weeks and 48-60 weeks post randomisationand will last approximately half an hour. Participants will also be contacted at 22-39 weeks to arrange delivery of an ambulatory blood pressure monitor. Participants will be reminded regarding the visits by text/email/post and a mutually convenient follow-up time arranged. Follow-up visits will be routinely undertaken remotely either by phone or videocall by the site research staff, but can be done in person if preferred. If the participant is uncontactable by telephone for the follow up visit after 3 attempts, the trial team will send the questionnaires via email and/or text for the participant to self-complete.
At these appointments, participants will either have their blood pressure checked (or check their own blood pressure) after 5 minutes rest using the provided blood pressure monitor. If tolerated by the participant, up to 6 blood pressure readings (with a minimum of 3 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 (where taken) 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. The approach of taking up to 6 readings attempts to reduce the potential bias that this habituation introduces.

At each follow-up appointment participants will be asked about:

- What anti-hypertensive medication they are currently taking
- Any side effects
- Any adverse events
- Concomitant medications
- Health-related quality of life using the EQ-5D-5L questionnaire
- The short form anxiety questionnaire (at 12 and 48-60 weeks only)
- Primary (GP/practice nurse) and secondary (hospital admission/outpatient visits) healthcare contacts
- Medication Adherence Report Scale Questionnaire (6 weeks only)

At 6 weeks only, a urine sample will be requested to test for urinary antihypertensive metabolites. A plain urine sample will be sent in a plain universal container without preservative using appropriate packaging through the post to the laboratory. Participants will be provided with a urine sample tube, sample taking instructions and a prepaid envelope to send the sample to the lab. A minimum of 1ml of urine is required for the analysis and as samples are stable for 3 days we will ask women to avoid sending samples on Fridays in case of delays over the weekend. It may also be necessary for sample dispatch to be avoided over

specific periods when the lab will be closed, in which case this will be communicated to participants. See Section 9.9 for details regarding sample handling.

Ambulatory Blood Pressure Monitoring (ABPM) (for primary outcome measurement): At 22-39weeks the participants will be required to wear an ambulatory monitor for a period of 24 hours (ambulatory blood pressure monitoring). The participants will be sent the ABPM unit directly from the central trial team, along with instructions of how to use the unit and how to return it. They will attach the monitor after a remote conversation with a trained member of the trial team, test the monitor and then wear it for the next 24 hours. Women will also be offered phone and video support for home fitting. Monitors will be returned to the central trial team by Royal Mail next day delivery service or by courier.

Once the monitors have been returned to the central trial team, a trial team member will download the results using the spacelabs software and transfer them using a secure download system to the PC-CTU. If the monitor did not collect enough readings for the primary outcome measurement, the participant will be contacted and asked if they would like to try the monitoring again. The central trial team will then reset the monitor for the next patient, clean the monitor following the manufacturers instructions and then send out ready for the next participant.

9.8.1 Qualitative sub-study follow up

Women

A purposive sample of approximately 30-40 participating women from both arms of the study will be invited to take part in longitudinal interviewing (at up to three time points, to include point of entry if practical and after the 22-39 week follow-up) to understand the day-to-day operation of the trial and impacts on daily life. Upon invitation, they will be asked if they would like to take part in the optional photovoice activity designed to support the interview(s). Should they decline to take part in the photovoice activity, they will still eligible to take part in an interview(s). In addition, we will include a sample of up to eight women who decide not to take part or withdraw, but who and are willing to be interviewed. We will recruit women from across the study sites and aim for a diverse sample, to help understand the real-life implementation issues with self-management postnatally. Purposive sampling will include women from central and peripheral hospital settings, a range of ages, socio-economic and ethnic background, parity, previous history of raised BP in pregnancy or pre-eclampsia. This will be assessed as participants start being contacted for the qualitative sub-study interviews.

Following consent to the qualitative study, semi structured interviews will be conducted with participants in both arms 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. Participants who consent to take part in the photovoice activity will have a short phone or video call with the qualitative sub-study researcher prior to the interview to discuss the activity in greater detail, including discussion around how to obtain permission for and safely take photographs. Participants will then take photographs on their smartphone that reflect their experiences of managing their blood pressure in the postnatal period. They will share these photographs with the

qualitative sub-study researcher prior to, or during, the interview by uploading them to a secure online folder in OneDrive. A link to this folder will be shared with the participant in an email. Photographs will then be looked at together by the researcher and the participant to aid reflection on the participant's experience of either usual care or self-management. Taking part in the photovoice activity will not require participants to undertake any additional interviews.

This embedded study will provide data regarding the views of participants as to the acceptability of self-monitoring and self-management in the routine management of gestational hypertension and pre-eclampsia after birth, once they have been discharged from hospital. The control group will be interviewed to allow comparison of participant experience in the two arms. Individuals who decline to participate in the main trial and those who subsequently withdraw from it, will still be invited to contribute an interview, as this will provide valuable insights into the acceptability of the intervention.

A subset of these interviews may be conducted by community-based researchers with translation where needed. The interviews will be at various time points during trial participation, allowing for flexibility around women's preferences. Interviews will be offered remotely (via telephone or videoconferencing) or face-to-face, with timing sensitive to the competing demands for a woman in the postnatal period, and last approximately 30-60 minutes. Interviews will be audio-recorded for transcription and analysis. We will offer text relay to support women who may have hearing conditions and to ensure non-English speakers are included, we will offer the use of an established telephone translation service such as 'Language Line'. Participants will be offered a voucher to thank them for their time.

Healthcare professionals

Semi-structured interviews will be conducted with 25-30 participating healthcare professionals (including obstetricians, midwives and GPs) involved in the study. Sampling for these interviews will be from across participating sites, and focus on ensuring staff perspectives provide insights into their experiences of using the intervention with diverse groups of women. Interviews will be offered remotely (via telephone or video-conferencing) or face-to-face and last approximately 30-60 minutes. Interviews will be audio-recorded for transcription and analysis. These will aim to understand how self-management is operationalised in practice.

9.9. Sample Handling

At the 6 week (+/-3) follow-up, participants will be asked to provide a minimum of a 10ml urine sample in a standard plastic container. Each sample will be transferred from the clinic site/participant's home to the laboratory at University Hospitals of Leicester at room temperature, via a Royal Mail next day delivery service. Samples remain stable for 72 h after collection.

All samples received by the laboratory will be analysed on a rolling basis. LC-MS/MS will be performed to detect all antihypertensive drug classes. The test is a standard laboratory test that is accredited by United Kingdom Accreditation Service (UKAS). Samples will be stored for up to 1 year after the end of the study declaration for quality checking/verification of the research, following which they will be stored for 5 years after the end of the study at a HTA licensed facility. The storage for 5 years after the end of the study is in case of future research, which participants will be asked to consent to.

9.10. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to discontinue early from the study intervention at any time. This may happen for several reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE related to the intervention.
- Inability to comply with study procedures
- Participant decision

Participants may choose to stop intervention and/or study assessments including urinary sample provision, but may remain on study follow-up.

Participants may also withdraw their consent to withdraw from the study completely. In the case of withdrawal from both treatment and active follow up, a participant's data and samples obtained up until the point of withdrawal will be retained for use in the study analysis. No further data or samples would be collected after withdrawal.

In addition, the Investigator may discontinue a participant from the study treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Clinical decision
- Loss of capacity to consent to involvement in research, for example due to developing puerperal psychosis
- Loss to follow up

Non adherence in either group would be defined as missing a trial visit, and not being contactable to reschedule the visit. Non adherence 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 adherence necessitating discontinuation 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 participant safety, and therefore will be influenced by the nature, frequency and clinical impact of a particular participant's non-adherence.
If a participant from the intervention arm discontinues from the study, they will continue usual postnatal care including blood pressure monitoring with their community midwife and GP.

The level of discontinuation or withdrawal and reason will be recorded in the CRF. If the participant discontinues or withdraws due to an adverse event, the Investigator will attempt to contact the participant's clinical care team for information until the adverse event has resolved or stabilised.

9.10.1 Qualitative sub-study

Women are eligible for this sub-study even if they withdraw from the trial. Healthcare professionals who choose to take part in the qualitative sub study will be free to withdraw if they decide they no longer want to take part.

Participants will be free to terminate a scheduled interview, the photovoice activity, or the interview itself at any point. Once they have participated in the interview they will have two weeks to withdraw from the study should they wish to; this will be made clear at the point of recruitment and at the end of the interview. If the participant withdraws from the sub-study within two weeks, their data (personal data, interview data including transcripts and recordings, and photographs if shared) will be securely destroyed. After two weeks, participant de-identified data will be incorporated into the body of the analyses but illustrative quotes from the interviews and any photograph taken by the participant will not be used in any outputs.

9.11. Health equity

Trial populations tend to include a larger proportion of affluent individuals than society as a whole. To address this, the SNAP2 trial aims to support health equity, in an effort to acknowledge that a lack of inclusionary practice can potentially increase health disparities and that outcomes for women are not equal. There remain stark gaps in maternity outcomes between women from Black, Asian, mixed and white ethnic groups and research aimed at improving care for women must seek to understand and address these disparities. Recognising that it is challenging to recruit participants from socially disadvantaged or ethnic minority groups unless proactive steps are taken to include them, we will engage with these communities throughout the trial to ensure that our materials are relevant and accessible to all women (Khunti K, 2020), (Prinjha S, 2020), (Darko, 2021) . We have engaged with third-sector organisations and community groups during the intervention and protocol development to ensure inclusion across the programme.

Trial recruitment: working with our co-applicants and PPI groups, inclusive recruitment routes have been devised aiming to ensure a diverse sample is included in the trial (Dawson S, 2022). This includes targeted selection of NHS trusts through which to recruit and engagement with community organisations. Electronic data collection will allow real-time assessment of the success of this approach, allowing iterative changes in process should initial results fall short of expectation. This builds on approaches used successfully in our previous pregnancy and postnatal trials which have recruited women representative (from an ethnicity perspective) of the wider pregnancy population. An information video will be created with a voiceover to explain the study in simple terms to aid recruitment.

Process evaluation (qualitative sub study): Understanding how the intervention has worked in practice for women and healthcare professionals from all parts of the population is important, particularly if the results from subgroups based on ethnicity or deprivation suggest any differences. Our qualitative work will include purposively sampling will ensure the experiences and perspectives of women from socio-economically deprived and/or ethnically diverse groups will be included.

Community based (peer) researchers: in order to ensure that the issues most important to women from diverse backgrounds are addressed in the process evaluation, community based (peer) researchers will be recruited through our PPI contributor networks and contracted on a consultancy basis. These community researchers will support research with minority ethnic groups that are often harder to reach in research. They will provide support to participate in up to 15 of the interviews described (plus translation costs). This will help to maintain the focus on health equity issues in the trial analysis.

Intervention and language: During intervention development we considered translation of the intervention. Latest census figures published by the government indicate that 3.1% of the population could not speak English at all ((ONS), 2021). These rates are highest among older groups (GOV.UK, 2020). Women aged 15-44 the range of people who couldn't speak English ranged from 0.1-2.8%, and those in the younger 10-24 age group the range was 0.1-0.7%. The usage of internet translation applications (e.g. Google Translate) or Language Line is highly prevalent. We have therefore concluded that it is reasonable to provide the intervention and study materials in English, using Inclusive Communication Guidance as a guide to plain English (GOV.UK, 2021).

9.12. Internal Pilot Phase and Stop Go Criteria

We will incorporate an internal pilot phase into the study. We will aim to recruit the first 100 participants within 6 months to prove that the trial is feasible. Following the 6 month period, the following Stop/Go criteria will be applied before transition to the main trial:

Table 1: Recruitment criteria in the first 6 months from 1st randomisation.

Number of participants recruited	Proposed Action
➢ 100 Participants	No change to trial
➢ 80-99	Careful review of trial procedures and inclusion criteria.
➢ 60-79	Careful review of trial procedures and inclusion criteria as above but substantial changes may be needed
➢ < 60	Discussion with sites, sponsor and funders regarding feasibility of continuing trial due to possible futility of recruitment.
• Recruitment per site: steady state of at least 1.5 women per month per site. Sites recruiting <1 women per month for 3 months in a row will be considered for decommissioning.	
• Proportion of those recruited from the relative deprivation/ethnic minority groups will be reviewed in the first 100 women. Although this will not be a formal stop/go criteria, adjustments will be made if the initial recruitment population appears not to be generalisable.	

9.13. End of Study Definition

The end of study is the date of the last data collection and cleaning prior to data lock or end of qualitative data collection, whichever is later. Samples will be stored for up to 1 year after the end of the study declaration for quality checking/verification of the research but the end of study date will be declared once all data collection and cleaning has been completed.

10. SAFETY REPORTING

10.1. Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant, which does not necessarily have a causal relationship with the trial intervention.
Serious Adverse Event (SAE)	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 a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. 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. Reporting Procedures for Adverse Events

Safety reporting will be from baseline to the 22-39 week follow up visit.

We do not anticipate that the study intervention (reporting of self-monitoring of BP via an app) should result in any adverse events (AEs), but include this section in case such events are reported at each study visit, so that they can be considered for causal links to the study.

Generally speaking, only unexpected adverse events* that are clinically judged (by the supervising site PI) as being caused by the trial intervention will be reported to the PC-CTU, who will inform the REC that gave favourable opinion in case of unexpected related serious adverse events. The supervising site PI should assess each adverse event's expectedness using the information below in Section10.3, and only report those which are judged to be unexpected. We will not ask for side effects as stated in the BNF to be reported as AEs, as these will be deemed expected adverse events.

*The only exception to this rule is that stroke, intracranial haemorrhage and seizure will always be reportable to the PC-CTU regardless of expectedness. Please also see Section 10.4.

Expected Adverse Events

The adverse events described below are expected to occur in this participant population and will not be classified or reported as SAEs, unless felt to be directly related to the study intervention. The CI will also review the AEs for expectedness – in cases of uncertainty, this will be ratified by the steering group.

- Admission for monitoring for hypertension
- Admission for psychiatric or social reasons
- Admission for postpartum complications (for example wound infection following surgery, mastitis, urinary tract infection)
- Known complications of postnatal hypertension that are collected for every woman as part of outcome collection
- Known side effects of prescribed medications as listed in the BNF
- Admission of the woman due to complications with the baby (including but not limited to neonatal jaundice, need for respiratory support, seizures, congenital anomaly)
- Pre-planned admission (e.g planned surgery)
- Side effects as stated in the BNF

10.3. Reporting procedures for Serious Adverse Events

Please see Section 10.3 regarding SAEs which will be reported as outcomes, so do not need to be reported as SAEs.

All serious adverse event (SAE) information must be reported on the PC-CTU SAE report form by the site and emailed to the trial inbox, 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 to confirm 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. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event.

10.4. 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 population, as they relate to the disorder being investigated (pregnancy and associated hypertensive diseases). These will be collected as outcomes and do not need to be reported as SAEs.

Potentially related to BP management	Unrelated to BP management
BP ≥ 160/110 mmHg BP < 90/50 mmHg whilst on treatment Faint Fall Headache Vomiting Upper abdominal pain	Vaginal bleeding Endometritis Sepsis Pyelonephritis Mastitis Surgical site infection Paralytic ileus Visceral injury (ureter, bladder, bowel) Pelvic collection Haematoma

Regardless of whether they might be expected in this population, the following serious adverse events will be reported as SAEs:

- Stroke
- Intracranial haemorrhage
- Seizure

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here. A detailed statistical analysis plan will be developed prior to randomisation of the first participant with prespecified sensitivity and subgroup analysis.

11.1.1 Description of the Statistical Methods

All analyses will be conducted in accordance with Oxford Primary Care CTU SOPs.

Internal pilot: Descriptive statistics will be used to describe recruitment of the first 100 participants (section 9.12).

In accordance with CONSORT guidelines, we will record and report participant flow. Descriptive statistics of recruitment, drop-out/withdrawal and completeness of intervention will be reported.

Baseline variables will be presented by randomised group using frequencies (with percentages) for binary and categorical variables and means (standard deviations) or medians (with lower and upper quartiles) for continuous variables. There will be no tests of statistical significance nor confidence intervals for differences between groups on any baseline variables.

The primary estimand is the mean difference in daytime ambulatory diastolic BP at 22-39 weeks for all randomised participants, as defined by protocol eligibility criteria, regardless of what intervention they actually received or adherence of intervention. A generalised linear mixed-effects model utilising data collected all time-points from randomisation will be fitted to the data with mean daytime diastolic BP measured at 22-39 weeks as the response variable, adjusting for minimisation factors for principal diagnosis (chronic hypertension or gestational hypertension/pre-eclampsia), mean postnatal diastolic blood pressure (last 3 readings in clinical record) (<83/≥83), number of anti-hypertensive medications (<2/≥2) and randomised group fitted as fixed effects and the model will include site as a random effect.
An adjusted mean difference at 22-39 weeks between the randomised groups, together with a 95% confidence interval and a P value, will be estimated from the model.

A similar approach will be used for continuous secondary outcomes, and generalised linear model for binary outcomes. Time effects will be included in the model for repeated measures outcomes where appropriate.

Safety outcomes will be compared using Fisher's exact or Chi-square test.

Pre-specified subgroup analyses of the primary outcome will be explored by baseline diastolic BP, principal diagnosis, ethnicity, indices of multiple deprivation quintiles, social status, and parity.

Standard residual diagnostics will be assessed for the appropriateness of the model.

11.1.2 Qualitative sub-study analysis

Interviews will be recorded, transcribed verbatim and de-identified. Interview and photographic data will be analysed using NVivo software. Analysis will be undertaken concurrently with data collection and conducted according to the standard procedures of rigorous qualitative analysis, which will include open and more focused coding, constant comparison and exploring deviant cases (Green, 2018). Analysis will be inductive, led by an experienced qualitative research fellow with close input from Hinton and regular discussions with wider team members and PPI representatives. A range of theories will be used to interpret these data. These will include Normalisation Process Theory (Murray E, 2010), and theories relating to responsibilisation and the burden to treatment (May CR, 2014), (Hinton L, 2021). Analysis will be used to iteratively develop an understanding of experiential and implementation barriers from the perspectives of participating women and healthcare professionals, and how self-management becomes embedded (or not) in both women's and healthcare professionals' routine work.

11.2. Sample Size Determination

Using data from the SNAP-HT feasibility trial and its follow-up study (Cairns AE, 2017), it is estimated that the standard deviation of mean daytime ambulatory diastolic BP at 6 months will be 10mmHg (inflated from 8mmHg to take into account greater heterogeneity between recruiting sites in this multicentre trial); 314 women (157 per group) are needed to detect ≥4mmHg difference (standardised difference 0.4) with alpha 0.05 and 90% power, and 15% post-randomisation drop out.

The aim will be to recruit approximately similar numbers of women with gestational hypertension/pre-eclampsia and chronic hypertension meaning that 628 women will be included overall. Assuming that the heterogeneity between these groups is small enough, 80% power will be retained for at least 5mmHg difference in diastolic BP for sub-groups of at least 40% of the total sample size, e.g. white vs non-white (expected 60:40 proportions). Furthermore, if appropriate to combine, the full sample of 628 women would allow smaller effect sizes to be detected (effect size = 0.22 – 80% power, effect size = 0.26 – 90% power).

During the regular monitoring of the trial, the TMG noted a higher proportion of gestational hypertensive women were enrolled in the study, (approximately 80%). In addition, the monitoring of ABPM completion showed low completion rates of ABPM (<50%). The sample size was subsequently inflated for operational reasons to retain the pre-specified power in the original sample size calculation in both gestational and chronic hypertensives as far as possible. Therefore, the sample size was updated to ensure 532 (266/0.5) gestational hypertensive women would be randomised and the remaining chronic hypertensive women to be recruited as far as possible in the recruitment period. Thus the recruitment period will allow approximately a total of 690 women.

11.3. Analysis populations

The primary analysis population will include all eligible participants for whom data is available. Participants will be analysed according to their randomised group assignment irrespective of the intervention they actually received or adherence of intervention. Participants who withdraw from the trial will be included in the analysis until the point at which they withdrew. Data from participants who withdraw from the intervention and or active follow-up will continue to be included in the analysis as far as the data are available.

Other analysis populations for secondary analysis will detailed in the SAP.

11.4. Decision points

There will be no planned interim analysis for efficacy and futility. Data on trial progress such as recruitment and participant drop-out of the trial and quality of data will be reported to both TSC and DMC as specified in the charters. Only the trial statistician and DMC will have access to unblinded results with blinded group allocation maintained throughout the trial until the analysis is complete.

The traffic light approach will be used for assessment of the internal pilot after recruitment of the first 100 women within six months to assess viability of the trial (section 9.12). Decisions regarding the success or otherwise of the internal pilot will be overseen by the TSC and DMC at around 7 months after the first participant has been randomised, to give time for data lock after 6 months.

11.5. Stopping rules

There are no predetermined stopping rules. Any consideration of the need for termination of the trial will be on the advice of the DMC to TSC who will make the decision whether or not to terminate the trial.

11.6. The Level of Statistical Significance

The level of significance will be set at 5% two-sided significance level. P-values will be adjusted for any multiple comparisons in order to maintain an overall type I error rate of 5%.

11.7. Procedure for Accounting for Missing, Unused, and Spurious Data.

Missing data in all outcomes will be inspected and reported, with reasons given where available and missing data mechanism explored across randomised groups. We will explore the mechanism of missing data, though the mixed effects model implicitly accounts for data missing at random. Factors found to be predictive of missingness will be included as fixed effects in the analysis models.

Additional sensitivity analysis using imputation methods, such as multiple imputation for data missing will be performed and a pattern mixture model for longitudinal data will be fitted to assess the robustness of the missing at random assumption required for mixed effect models.

11.8. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

The final statistical analysis plan will be agreed prior to final data lock and prior to any analyses taking place. Any deviation thereafter will be reported in the final trial report.

11.9. Health Economics Analysis

11.9.1 Health Economic Analysis Plan (HEAP)

The health economic aspects of the study are summarised here. A detailed health economic analysis plan will be developed prior to data lock.

11.9.2 Within-trial economic evaluation

An economic evaluation using an NHS perspective will be conducted as an integral part of the SNAP2 trial. This analysis will take the form of a cost-consequences analysis and will utilise participant-level data collected during the trial to determine whether there are differences in costs and participant health outcomes between treatment arms over the first 12-months of intervention implementation.

We will collect health care resource use and health-related quality of life data using participant questionnaires at baseline, 12, 22-39 and 48-60 weeks follow-up. In terms of resource utilisation, we will capture details of antihypertensive medications prescribed, hospital inpatient admission and outpatient visits, and primary care contacts. Unit costs to value these healthcare contacts will be obtained from established national sources, including the National Schedule of NHS Costs and the Personal and Social Services Research Unit (Curtis, 2020). A bottom-up costing approach will be employed to estimate the healthcare costs associated with self-management (e.g. the home blood pressure monitor, participant training in the use of the monitor and app, and physician time spent reviewing and approving medication

changes). Participant health-related quality of life will be assessed at trial entry and each follow-up using the EuroQol EQ-5D-5L instrument (Herdman, 2011). Value sets to derive utility scores for EQ-5D-5L states are currently under development for a UK setting but should be finalised by the time of the analysis.

Mean (standard deviation) estimates of resource use, costs and quality of life will be reported separately for each trial arm. When comparing between trial arms, mean differences (95% confidence intervals) calculated using regression methods adjusted for key baseline characteristics, will be used. We will use multiple imputation to deal with missing data and will present within-trial results for key sub-groups as specified by trial's clinical team.

11.9.3 Model of longer-term costs and effects of BP self-management and usual care versus usual care alone

Better blood pressure control post-pregnancy offers the potential for lower blood pressure and a reduced risk of cardiovascular disease and stroke over the longer-term. We will therefore utilise health economic modelling to extrapolate the longer-term costs and consequences of any reduction in post-pregnancy blood pressure observed with self-management during the trial. We will adapt a decision analytic Markov model we previously developed to simulate the long term costs and outcomes of blood pressure self-monitoring during pregnancy, and from an NHS perspective, will simulate lifetime healthcare costs and quality-adjusted life years (QALYs) of blood pressure self-management versus usual care alone.

The model will comprise a number of mutually exclusive health states including an 'alive and well' state and various cardiovascular event states. The cohort entering the model will be matched in characteristics (e.g. age, ethnicity, BMI, type of hypertension, blood pressure etc.) to participants in the SNAP2 trial and published data will be used to estimate how the cohort transitions between the health states on an annual basis. Annual risks of a first cardiovascular event for example will be estimated by entering cohort characteristics into established prediction tools such as Framingham and Q-Risk, and then further augmenting these predictions for the additional risks associated with pregnancy hypertension and its adverse events. The treatment effect, modelled as a reduction in predicted cardiovascular risk attributable to a lowering of diastolic blood pressure, will be informed by the trial data. The health-related quality of life and cost implications of the various cardiovascular disease events will be sourced from the published literature and included within the model.

Running the model will generate predicted lifetime mean healthcare costs and QALYs with self-management and with usual care. A comparison between model arms will be made and results expressed using an incremental cost per QALY gained. This figure will be compared to current thresholds for value for money (NICE, 2008). Uncertainty surrounding the model's input parameters and results will be handled using probabilistic sensitivity analysis and presented using cost-effectiveness acceptability curves. Sensitivity analysis will explore the implications of varying the analysis time horizon upon uncertainty and the cost-effectiveness results. The model will be constructed such that the characteristics of the cohort entering the model can be altered and cost-effectiveness explored for subgroups differentiated for example by ethnicity or social deprivation.

All analyses will be conducted in line with current good practice guidance on undertaking and reporting the findings of economic evaluations and decision analytic models (Caro, 2012) .

12. DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital and primary care records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, participants' blood pressure records, laboratory and pharmacy records, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent form and the contact details database, the participant will be referred to by the study participant number/code, not by name.

12.2. Access to Data

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

12.3. Data Recording and Record Keeping

All trial data will be entered on eCRFs wherever possible. Where use of paper is inevitable, this will be transferred to the eCRF/database as soon as possible. Sites will be asked to take a copy of the paper CRF and send the original back to the trial office where this will be stored in a locked filing cupboard within the CTU.

The participants will be identified via a unique trial specific number. The participant's name,address, NHS number, email address and phone number will need to be recorded for trial follow up purposes. Identifiable data that has not been pseudonymised and NHS number will be retained for 10 years to allow for approach about future research (further funding dependent), where participants have consented to this, this will be stored separately from other trial data. Otherwise, this data will be deleted when all follow-up visits for the participant in question have been completed. Anonymised data will be retained indefinitely for meta-analysis.

Data Management will be performed in accordance with PC-CTU Data Management SOPs which are fully compliant with Good Clinical Practice (GCP). Study specific procedures will be outlined in a DMP to ensure that high quality data are produced for statistical analysis. The DMP is reviewed and signed by all applicable parties including the Trial Manager and the Trial Statistician, prior to the first participant being enrolled.

CRFs will be completed electronically using a secure validated web based system - the trial intends to use the REDCap eCRF system. The system will incorporate data entry and validation rules to reduce data entry errors, and management functions to facilitate auditing and data quality assurance. Data protection requirements will be embedded into the design of the web-based system and enforced by best practice trial management procedures. The Data Manager will oversee the process of electronic data validation and manual listings, sending out queries when required and following these up until the queries are resolved. CRFs may also be completed in paper format if required.

A separate REDCap database will be used to securely store all identifiable participant information required to contact participants and permit follow up. Access to this information will be strictly on a need-to-know basis and databases will be password protected on a secure server.

On completion of the trial and data cleaning, the study documentation will be transferred to a secure, GCP compliant archiving facility, where they will be held for 20 years. Participants' identifiable information (other than NHS Number and Consent Form) will be destroyed at the end of the trial. The only exception to this rule is where participants have consented to have their name and contact details retained, so that they may be contacted regarding future research. Prior any database lock, the Data Manager and the Trial Statistician will undertake a dataset review as specified in the DMP. The CI is responsible for authorising retrieval and disposal of archived material.

The Clinical Trial Unit will preserve the confidentiality of all data obtained which are to be kept by the SNAP2 research team in compliance with the Data Protection Act 2018 (DPA), General Data Protection Regulation (GDPR) and PC-CTU Data Management SOP - this includes personal data of all participants.

12.3.1 Qualitative sub-study

For the qualitative sub-study interviews, digital data (e.g. interview audio recordings, photographs, electronic consent forms and electronic scans of paper versions) will be transferred to password-protected storage on University of Oxford computers/servers as soon as possible after collection and deleted from portable devices. Interview audio recordings will be given a unique identifier, encrypted and password-protected before being sent securely (via a University owned file transfer interface requiring authentication) to approved transcribers at the University of Oxford, who have confidentiality and data protection contracts and a completed third party security assessment in place. Transcripts will be returned the same way. Transcribers will delete audio files and transcripts from their encrypted computer following completion of transcription. Interviews will be transcribed verbatim and de-identified at the earliest opportunity by the researcher. De-identified data will be stored in computer files on partitioned, password-protected University servers. Paper consent forms will be stored in locked filing cabinets at the Nuffield Department of Primary Care Health Sciences, University of Oxford. Once photographs have been uploaded by participants to a secure online folder, they will be downloaded and held on password-protected University servers. One downloaded, they will be securely deleted from the secure online folder. Photographs will be given an identifier to match their corresponding interview, and will not be shared with individuals outside the study team. Contact details will be stored in separate password protected folders and the ID numbers/identifier key in a separate password-protected sub-folder only accessible to members of the study team. Qualitative data analysis software (NVivo) will be employed to manage data

and generate 'reports' containing all the relevant data across cases/themes. Audio files will be deleted at the end of the study. De-identified research data will be shared between members of the study team (co-investigators and researchers who report to them, including those yet to be appointed) by granting access to password protected storage on University of Oxford computers/servers or through using encryption and password protection as described above for data transfer to transcribers. Transcripts, photographs and demographic data will be retained for IPD and qualitative secondary analyses for up to 20 years.

13. QUALITY ASSURANCE PROCEDURES

13.1. Risk assessment

A risk assessment and monitoring plan has been prepared and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities. Monitoring will be performed by the PC-CTU Quality Assurance Manager or delegate. The level of monitoring required will be informed by the risk assessment.

13.2. Study monitoring

Regular monitoring will be performed according to the study specific Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the study specific Monitoring Plan. Following written standard operating procedures, study staff with delegated monitoring responsibilities will verify that the clinical study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

13.3. Study Committees

The composition, roles and responsibilities of committees are detailed in their respective charters, their basic functions are as follows:

Trial Management Group (TMG) - will be responsible for the day-to-day running of the trial, including monitoring all aspects of the trial and ensuring that the protocol is being adhered to. It will include Co-Investigators and will meet as per the charter .

Trial Steering Committee (TSC) - will ensure the rights, safety, and wellbeing of the trial participants. They will make recommendations to the funder about how the trial is operating, any ethical or safety issues and any data being produced from other relevant studies that might impact the trial. Composition, and roles and responsibilities of the TSC are detailed in the TSC charter. The TSC advises the TMG about the conduct of the trial. Frequency of meeting will be agreed with the TSC and specified in the TSC charter.

Data Monitoring Committee (DMC) The role of the DMC will be to review the data to safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, to ensure

continued trial integrity, scientific value, and ethical treatment of study subjects and monitor the overall conduct of the clinical trial. Composition, roles and responsibilities, and frequency of meetings of the DMC are detailed in the DMC charter.

14. PROTOCOL DEVIATIONS

A study-related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file. Where required, sites will be asked to provide details of corrective and preventative actions.

The investigator is not allowed to deviate from the protocol except in the case of an urgent safety measure to protect clinical trial participants from any immediate hazard to their health and safety, in which case such deviations shall be documented and reported to PC-CTU **as soon as possible**.

A PC-CTU SOP is in place describing the procedure for identifying non-compliances, escalation to the central team and assessment of whether a non-compliance /deviation may be a potential Serious Breach.

15. SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

Investigators must notify the trial team **within 1 working day** if a serious breach is suspected. In the event that a serious breach is suspected, the Sponsor must be contacted **within 1 working day**. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

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

16.2. Guidelines for Good Clinical Practice

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

16.3. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions 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.

16.4. Other Ethical Considerations

The main ethical issues associated with this research are confidentiality, informed consent, ensuring that participation does not lead to inferior care and ensuring women are not inappropriately contacted following still birth or any other poor outcome.

Confidentiality of potential participants in the programme will be maintained through scrupulous data management and careful communication.

Consent will be taken only after potential participants have had an opportunity to consider whether to take part in the study and randomisation will occur after birth. Women will be supported to make an informed choice and can be approached prior to birth if appropriate. Women will be free to discontinue or amend their participation in the study at any stage. Importantly, all interventions will be in addition to standard care so no participating women will receive inferior care compared to usual care.

Women in both randomisation groups will receive postnatal management by their community midwife and GP following their discharge from hospital. If women in the intervention arm still require additional support from the GP or community midwife postpartum for other medical, mental health or social issues then this will continue irrespective of their involvement in the trial.
Any incidental findings that arise as a result of study procedures or investigations will be communicated directly to participants by the site PI or 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.

Women who suffer an adverse perinatal outcome (Neonatal 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 the approach will be considered sensitively. This follows direct advice and input from lay representatives who have experienced such outcomes.

For the qualitative sub-study using interviews with women and health professionals, it is recognized that asking questions around postnatal care may cause discomfort to some participants. Interviews will be conducted by experienced qualitative researchers and questions will be asked with utmost sensitivity. Respondents will be assured of confidentiality and be informed that they are free not to respond to questions that cause them discomfort, and that they can discontinue the discussion at any point. It is possible that issues of ethical concern might arise or be raised in the course of interviews. In such cases, respondents will be given information on possible support services/resources.

Ethical considerations around the capturing and use of photographs as part of the photovoice activity in the qualitative sub-study have also been considered. Alongside guidance in the participant information sheet, participating women will have phone or video call prior to their interview to discuss ethical practices for the activity. Women will be asked to seek verbal permission from people before taking their photographs. If a person in a photograph is under 16, a parent or guardian must also provide permission. If women take pictures in crowded public places, it will not be feasible for them to seek permission from every person in the photograph. Therefore, if panoramic photographs are taken in a way which do not focus on specific subject, permission will not be needed. If taking photographs in public places such as a cafe or library, women will be advised that they should seek permission from the relevant person(s) to do so. Women will be advised to consider their own safety when taking photographs, by thinking about where they are taking photographs (for example not taking a photograph whilst crossing the road), and what they are taking photos of. They will be advised not to take photographs of illegal or dangerous activities. Women will be asked to not take photographs that contain identifying features of people or places. For example, we will ask them to not take or share photographs that show people's faces. Ultimately, it is the participant's choice as to the photographs they take and share. Should a photograph containing identifying features of a person or place be shared with the research team, these will be blurred by a member of the research team and the original copy of the photograph securely deleted. To further maintain participant confidentiality, only photographs that do not contain information that could identify the people or places depicted in the photographs will be used when reporting the results of the study.

16.5. Reporting

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

16.6. Transparency in Research

The study will be registered on the International Standard Randomised Controlled Trial Number (ISRCTN) registry prior to the recruitment of the first participant.

The trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial date, as specified on the end of trial declaration.

16.7. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the informed consent forms where participant name and initials will be added. For the qualitative study, contact information for the

participants and clinicians participating will be stored only until the final interview has been completed. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data. For those particiapnts who give consent to store their contact details for future research, these details will be stored in a secure separate database for up to 10 years. Transcribers will delete audio files and transcripts from their encrypted computer following completion of transcription. Interviews will be transcribed verbatim and de-identified at the earliest opportunity by the researcher. De-identified data will be stored in computer files on partitioned, password protected University servers. Photographs will be stored on a partitioned, password-protected University server. Any faces or identifiable details captured in photographs will be blurred by a member of the research team using Microsoft PowerPoint, and the original unedited copy of the photograph will be securely deleted. Only photographs that do not contain information that could identify the people or places depicted in the photographs will be used when reporting the results of the study.

16.8. 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. Participants that complete the ABPM will receive a £25 voucher. Those participants taking part in the qualitative part of the study will receive a £20 voucher for their time. The Participant will not be required to send their blood pressure monitor back once the trial has ended.

17. FINANCE AND INSURANCE

17.1. Funding

This study is funded by NIHR Programme Grants for Applied Research

17.2. 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 that is provided.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

A publication plan will be drawn up and agreed prospectively. The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. This protocol is part of an activity that has received funding from the NIHR. Authors will acknowledge that the study was funded by NIHR Programme Grants for Applied Research. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The protection and exploitation of any new IP is managed by the University's technology transfer office, Oxford University Innovations. Separate agreements will be arranged, as applicable between the University and participating diagnostics providers to detail rights to access data produced in the SNAP2 study.

20. ARCHIVING

All essential documents will be archived for at least 20 years, and in accordance with the PC-CTU's Archiving SOPs. The CI is responsible for authorising retrieval and disposal of archived material.

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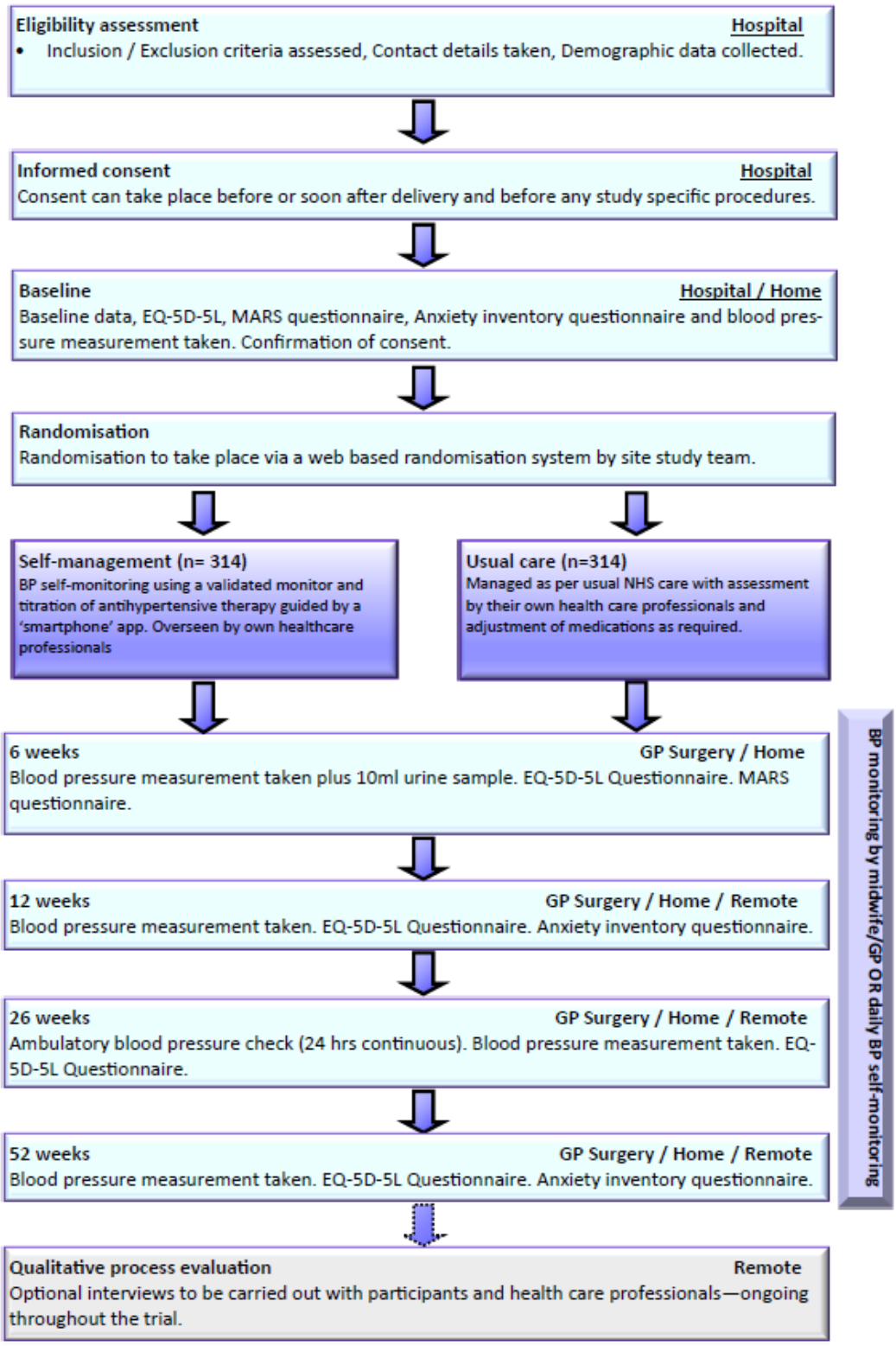
APPENDIX A: STUDY FLOW CHART



APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures	**Visits**					
	Screening	**Baseline**	**2:** 6 weeks +/- 3w	**3:** 12 weeks +/- 4w	**4:** 22-39 weeks	**5:** 48-60 weeks
Informed consent	X					
Demographics		X				
Medical history		X				
Eligibility assessment	X					
Eligibility confirmation	X					
Randomisation		X				
Blood pressure check	X		X	X	X	X
Ambulatory blood pressure check					X	
Document medications		X	X	X	X	X
Side effect check			X	X	X	X
Adverse event assessment			X	X	X	X
EQ-5D-5L		X	X	X	X	X
MARS Questionnaire		X	X			
Urine Sample			X			
Short Form anxiety inventory questionnaire		X		X		X
Healthcare Resource Use		X		X	X	X

APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
SA 1	2.0	15Aug2024	Sophie Betteridge	1. Amendment to the Urine sample instructions to reflect slight change in process 2. Addition of patient facing trial posters x 4 3. Addition of My BP Care App Patient Walkthrough 4. Amendment to Intervention Advice for Clinicians- administrative 5. Addition of BP Monitor Instruction Card
SA 2	V2.0	05Feb2025	Ellie Newbury	1. Addition of ambulatory blood pressure monitoring instructions for participants. A shortened version of the instructions is also included. 2. Addition of text message scripts for the trial team to send to the participants relating to the ambulatory blood pressure monitoring. 3. Addition of text message/email scripts for the trial team to send to the participants that sites have been unable to get hold of for the follow-up appointment 4. The PIS is updated to reflect the changes introduced in this amendment. 5. Administrative update to the PIS to update name of Trial Manager to Ellie Newbury.
SA 3	3.0	19May2025	Ellie Newbury	1. Update to processes and documentation for ambulatory blood pressure monitoring.

				2. Addition to photovoice activity to the qualitative sub-study. 3. Addition of option for the follow up CRFs to be completed as participant completed quesitonnaires. 4. Addition of community midwife letter. 5. Addition of GP letter regarding participants that have not acted on high/low blood pressure readings they have input onto the My BP Care app. 6. Update to the follow up reminders sent to participants. 7. Administrative updates to the protocol.
SA 4	4.0	08Oct2025	Ellie Newbury	1. Update to sample size to at least 532 women with gestational hypertension, resulting in a total, including with women with chronic hypertension, of approximately 690. 2. Update to follow up timepoints (26 week changed to 22-39 weeks and 52 week changed to 48-60 weeks). 3. Clarification that follow up timepoints are post randomisation.

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC / HRA submission.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).