Combined monitoring for hypertensive pregnancy: A feasibility trial

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Conflicts of interest: R.M. has received BP monitors for research use from Omron and is working with them to develop a telemonitoring system for use in primary care. The BUMP+ app was adapted for commercial use by Sensyne. RM receives no personal payment for such work. The remaining collaborators have no disclosures.

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

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1. KEY CONTACTS

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Committees	For this small pilot study we will have a combined trial and data-monitoring committee. **Trial and Data Monitoring Committee** **Chair**: Jenny Myers (Obstetrician), Jenny.Myers@manchester.ac.uk **Committee members**: PPI representative, Statistician.

2. LAY SUMMARY

High blood pressure (hypertension) is becoming increasingly common, especially among younger people. Currently 1 in 20 pregnancies occurs in a woman who has longstanding hypertension, for which they are usually taking medication to control. If a pregnant woman has longstanding high blood pressure, there is a 1 in 4 chance that she will develop pre-eclampsia. Pre-eclampsia is a serious condition which is diagnosed by a rising blood pressure and protein in the urine. Currently, pregnant women with hypertension have frequent clinic appointments for monitoring, and make any changes needed to their blood pressure medications. Early detection of rising blood pressure and / or protein in the urine can reduce the risk of future complications for mother and baby.

There have been recent trials investigating the use of self-monitoring of blood pressure in pregnancy, where women check their blood pressure readings daily at home, and use these to guide their management. These have been shown self-monitoring to be safe, cost effective and well-received by participants, but more research is needed into how to use it to improve outcomes. This study will ask participants to self-monitor their blood pressure daily, test their urine weekly for protein, and submit these readings into a mobile phone app. Via the app, their healthcare team will be able to recommend if an increase in their medication is needed based on their readings, or if an urgent clinical review is required, with the aim that earlier detection of changes will improve outcomes. This study is to assess the feasibility of this process, before the development of larger scale clinical trials to investigate the impact on outcomes.

3. SYNOPSIS

Study Title	Combined monitoring for hypertensive pregnancy: A feasibility trial		
Internal ref. no. / short title	My Pregnancy Care		
Study registration	The study will be registered on the ISRCTN before the 1st participant is recruited.		
Sponsor	University of Oxford, Research Governance, Ethics & , University of Oxford Joint Research Office, Block 60, Churchill Hospital Oxford, OX3 7LE RGEA.Sponsor@admin.ox.ac.uk		
Funder	National Institute for Health Research (NIHR) Programme Grant for Applied Health Research Ref: RP-PG-0614-20005		
Study Design	Multi-centre Randomised Controlled Trial		
Study Participants	Pregnant women* with hypertension		
Sample Size	60 women – 40 in intervention arm, 20 in control arm		
Planned Study Period	The planned total duration of the project is 12 months. The duration of individual involvement will be 28 weeks.		
Planned Recruitment period	01/02/2024 – 31/12/2024		
	Objectives	Outcome Measures	Timepoint(s)
Primary	How feasible is self-monitoring of hypertension, self-testing for proteinuria and remote titration of medication in a group of pregnant women with hypertension?	• Recruitment rate per site (number approach vs number recruited) • Adherence and persistence to self-monitoring protocol • Adherence and persistence to self-testing for proteinuria • Loss to follow-up	End of study
Secondary	Does the use of self-monitored BP readings with self-titration improve BP control during pregnancy in women with hypertension?	Difference in mean and mean highest systolic blood pressure between groups post-randomisation.	End of study
	What is the safety of a self-monitoring, self-testing and self-management intervention in this context?	• Reporting of serious adverse events and side effects. • Number of adverse events.	End of study

Intervention(s)	Daily self-monitoring of blood pressure + weekly protein testing + 1 step titration increase in medication if needed based on home readings (with clinical check)
Comparator	Usual antenatal care

*We have used the term pregnant women throughout this protocol. This includes all people who are pregnant.

4. ABBREVIATIONS

BP	Blood pressure
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
NHS	National Health Service
RES	Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PE	Pre-eclampsia
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RGEA	Research Governance, Ethics & Assurance
SMBP	Self-monitored Blood Pressure
SOP	Standard Operating Procedure

5. BACKGROUND AND RATIONALE

Raised blood pressure (BP) affects approximately 10% of pregnancies worldwide (1), and around 25-35% of these affected women develop pre-eclampsia (2). Globally, around 15% of maternal mortality is due to pre-eclampsia so early detection and prevention is paramount.

Inadequate management of raised BP, in particular systolic hypertension, was a key finding requiring action in the 2005-2008 UK Confidential Enquiry into Maternal Deaths (3). Although more recent MBRRACE reports showed that deaths associated with hypertension in pregnancy have dropped, pre-eclampsia remains important.

Once raised BP is detected during pregnancy, the clinical focus is to control BP within optimal range, as well as regular monitoring to promptly detect the development of pre-eclampsia and ensuring appropriate foetal surveillance is undertaken (4). Pre-eclampsia is characterised by raised BP at 20 weeks gestation or greater, with the detection of protein in the urine. Substantial resources are currently expended in monitoring women with raised BP at antenatal appointments with obstetricians and midwives, both from the woman's and the National Health Service' (NHS) perspective.

Antenatal checks take place every four weeks at the start of pregnancy, moving to every two weeks towards the end of pregnancy. Women who are at higher risk for raised BP in pregnancy (e.g. due to age or previous medical history) require more frequent monitoring and are likely to have weekly visits towards the end of pregnancy (5). BP can rise rapidly in pregnancy and hypertension may go undetected in between antenatal visits, despite the current extra clinic monitoring in place.

Self-monitoring has the potential to support improved BP management, reducing maternal morbidity and mortality, whilst at the same time increasing women's involvement in their own care. Self-monitoring of BP is now common place in adults with hypertension (6, 7). Previous research has shown that self-monitoring of BP is safe and cost effective in hypertensive pregnancy, but self-monitoring alone did not improve the management of hypertension (8). Previous work outside of pregnancy has shown that co-interventions can improve BP control (9). One strategy is remote antihypertensive medication titration based on self-monitoring readings, which has been found to be effective at improving BP control in non-pregnant populations (10, 11), but has yet to be trialled in pregnant women.

Self-testing for proteinuria has been shown to be just as accurate as health care professional testing and could support remote care of hypertensive women. Indeed, around half of maternity units surveyed in the pandemic were offering proteinuria self-testing alongside BP monitoring (12).

A variety of strategies have been employed to communicate self-monitoring results to clinicians, including SMS text services, mobile apps and wireless monitoring devices. Interventions using mobile phone apps seem promising, and have been well received in previous studies investigating BP self-monitoring in pregnancy by participants and healthcare professionals. They allow easy input of BP readings with rapid feedback to patients of any further steps required. However, using an app to facilitate changes to medication doses based on self-monitoring readings is a new area of interest, as it has the potential to significantly reduce the requirement for outpatient appointment attendance for patients and reducing clinician workload. It also could improve medical management by earlier detection in BP changes, alongside more prompt medication changes, hopefully improving clinical outcomes.

The app has been developed by the study team at the University of Oxford. The app is based on development, which has previously been trialled (BUMP trials REC: 17/WM/0241 and the DAPHNY study, REC: 22/WA/0130). The look and content of the APP was develop in a separate study (REC: 22NW0175) with input from both pregnant and recently pregnant participants and health care professionals involved in antenatal care.

The app has been developed by the study team at the University of Oxford, and the backend servers will be hosted by NHS servers, located on the OUH site in Oxford. A security assessment was performed for our previous trial, and the current technological stack has not been modified.

5.1. Aims

This study aims to assess the feasibility of self-monitoring of BP, self-testing of urine for proteinuria and remote titration of antihypertensive medication via an app for those with hypertension at 20 weeks pregnant or greater.

5.2. How will the results of this study be used?

Self-monitoring of BP, self-testing of urine and remote antihypertensive medication titration has the potential to be a successful strategy in the management of gestational hypertensive disorders and earlier detection of pre-eclampsia. The results of this could be applicable to many thousands of women in the UK and beyond. We anticipate that the results of this trial will be used to inform guidelines for antenatal care.

5.3. Potential Risks

During this randomised controlled feasibility trial (RCT), 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 obtaining an excessively high or low self-monitored BP reading, and not appropriately escalating this to a healthcare professional. Even if these readings are assessed suitably, they could lead to increased maternal anxiety due to the study. Training of participants will cover repeating measurements in the case of unusually high or low readings, as well as how and when to seek medical support should they occur. The participant instruction booklet will provide information about BP and proteinuria testing and give clear advice to women to contact the antenatal care team or other healthcare professional (e.g. General Practitioner (GP)) in the case of maintained high or low BP readings or a positive proteinuria result. The app system will automatically re-state this advice when high or low readings are sent in. Women will continue to be seen as per standard care by their clinical teams (midwives/GPs/obstetricians) throughout regardless of randomisation group.

5.4. Potential Benefits

Potential benefits for inidividuals taking part include better information about their BP and the possibility that worsening hypertension or pre-eclampsia could be recognised earlier than it would have been with standard care alone. Trial results will provide information about the diagnosis of hypertension during pregnancy to inform future antenatal care.

6. OBJECTIVES AND OUTCOME MEASURES

<table>
<tr><th>Objectives</th><th>Outcome Measures</th><th>Timepoint(s) of evaluation of this outcome measure</th></tr>
<tr><td>Primary Objective
How feasible is self-monitoring of hypertension, self-testing for proteinuria and remote titration of medication in a group of pregnant women with hypertension?</td><td>Recruitment rate:
Number of participants recruited per site per month, including as a proportion of those who were approached and eligible
Loss to follow-up:
Number lost to follow-up rate / number of participants randomised
Withdrawal rate:
Number discontinuing from self-monitoring/number of participants randomised to self-monitoring
<u>Intervention arm only:</u>
Adherence and persistence with self-monitoring BP protocol:
Number of home BP measurements/protocol total measurements for time in study
Proportion persisting with home BP measurements (at least one reading per week) by week
Adherence to remote titration of antihypertensive medication where indicated:
Number of medication changes in response to high readings / number of high readings resulting in a request to increase medication
Adherence and persistence with self-testing for proteinuria:
Number of home testing results/protocol total measurements for time in the study
Proportion persisting with home BP measurements (at least one reading per week) by week</td><td>End of Recruitment

End of the study.</td></tr>
</table>

Secondary / exploratory Objectives	Outcome Measures	Time point of this measure
Does the use of self-monitored BP with remote titration of antihypertensive medication improve BP control during pregnancy in women with hypertension?	Difference in mean and mean highest systolic blood pressure between groups post-randomisation during the duration of the study Proportion of readings bellow 135/85 (clinic readings)	End of the study
What is the self-reported medication adherence amongst pregnant women with hypertension comparing BP self-monitoring and usual care groups?	Medication adherence and persistence recorded using repeat MARS-5 questionnaires for each group (13)	During and at the end of the study
What is the effect of BP self-monitoring on antihypertensive medication prescribing?	Difference in Defined Daily Dose of antihypertensive medication between intervention and usual care group	End of the study
Women's and clinician's experience of the BP self-monitoring intervention	Antenatal and postnatal EQ-5D-5L (14) and short-STAI participant quality of life questionnaire (15) A short questionnaire about self-monitoring BP at the end of the study	During and at the end of the study
Women's and clinicians' experience of remote titration of antihypertensive medication	Proportion of recommended antihypertensive medication changes accepted by clinician and participant Questionnaire	End of the study
What is the safety of a self-monitoring, self-testing and self-management intervention in this context?	Reporting and number of adverse events	Ongoing through the study

The following table shows which measurement tools will be used at the different time points:

	Baseline	1st follow-up contact (30 weeks gestation)*	2nd follow-up contact (8 +/-3 weeks post del)
MARS-5 questionnaire	✓	✓	✓
EQ-5D-5L questionnaire	✓	✓	✓
Short-STAI questionnaire	✓	✓	✓
Postnatal questionnaire about Self-monitoring of BP			✓
Questionnaire on experience of remote medication titration			✓

*or after 2 weeks if starting after 30 weeks

7. STUDY DESIGN

This multi-centre randomised controlled feasibility trial is a study of self-monitoring of BP with self-testing of proteinuria during pregnancy, combined with remote titration of antihypertensive medication.

Pregnant people with hypertension will be recruited from secondary care antenatal clinics in the UK. The study will involve two sites. Pregnant people will be recruited from around 20 weeks gestation and followed through pregnancy until 8 weeks postpartum.

Baseline visit: questionnaire including information on participant's past medical history, previous and current medications, pregnancy history, risk factors for pre-eclampsia; including family history, lifestyle factors and demographic data. Baseline parameters will be collected; height, weight at booking, blood pressure and urinalysis results. Participants will be provided with a BP monitor and protein dipsticks and taught how to use the BP monitor and test their urine for protein. They will be supported in downloading the app, registering their information, and shown how to submit BP and urine results.

Follow up contact 1: questionnaire (by phone call, email, in person) at around 30 weeks gestation or around 2 weeks after starting the intervention if randomised later than 30 weeks, undertaken by the research team.

Follow up contact 2: questionnaires and collection of the loaned BP monitor (in person, by post and/or over the phone) at around eight weeks following delivery undertaken by the research team. A notes review will be undertaken following the primary discharge for mother and baby. If a woman is still in hospital at 2 months and/or her baby at estimated date of delivery or 2 months (whichever is longer), the admission will be censored and data collected up to that point.

See study flow chart appendix A.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Pregnant women with hypertension will be invited to take part from around 20 weeks gestation (+/- 4weeks).

8.2. Inclusion Criteria

The participant can enter the study if all the following apply:

- Participant is willing and able to give informed consent for participation in the study
- Pregnant woman aged 18 years or over
- Diagnosis of hypertension (blood pressure previously sustained at ≥140/90mmHg)
- From 20 weeks (+/-4 weeks) gestation, up to 34 weeks gestation
- Currently prescribed one antihypertensive medication
- Currently negative protein on urine dipstick testing

8.3. Exclusion Criteria

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

- Women whom the midwife or obstetrician feel that it would be inappropriate to approach, for example those acutely unwell
- Participant does not wish to self-monitor / self-manage their blood pressure
- Abnormal uterine artery doppler results in this pregnancy
- Early onset (<34 weeks gestation) pre-eclampsia in a previous pregnancy
- Imminent delivery

9. PROTOCOL PROCEDURES

9.1. Recruitment

Secondary care centres in the UK will be selected to take part to represent different populations and on willingness to take part.

Healthcare professionals will screen notes/records for women who are likely to be eligible for the trial. These women will be approached and provided with study information. Potential participants will be provided with study information at any time from early pregnancy (at their first antenatal care visit) up until 20 weeks gestation. Women interested in taking part will be invited to attend a study visit at around 20 weeks gestation (+/-4 weeks), at which they will be able to ask questions about the study. Where possible this visit will take place alongside a standard antenatal visit. This first study visit could take place several weeks from provision of information or may take place on the same day at the convenience of the participant, provided the woman is content that she has had sufficient time to consider the study.

Once a participant has consented to take part in the study, a formal eligibility assessment, baseline information and questionnaires will be recorded. The participant will then be randomised to control or intervention groups.

9.2. Screening and Eligibility Assessment

Screening and randomisation may take place within the same study visit (but not necessarily), if the woman chooses to do so. Health care professionals will screen the notes/records to assess eligibility of women and select who will be offered a patient information leaflet if interested. They will also obtain verbal consent to pass their details to the research team. These women will be approached (in person, by phone or by email) and invited to a baseline assessment.

During the baseline assessment a full eligibility assessment will take place using the inclusion and exclusion criteria as described in 7.1.2 and 7.1.3.

9.3. Informed Consent

Participant Information and Informed Consent will be presented to the participants detailing the nature of the study; what it will involve for the participant; 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 be allowed as much time as they want (up to 34 weeks gestation), to consider the information, and the opportunity to question the Investigator, or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained. The person who obtains consent must be suitably qualified and experienced and have been authorised to do so by the Chief/Principal Investigator. One copy of the signed Informed Consent will be given to the participant, one copy will be stored in the participant notes and the original will be retained at the study site.

9.4. Randomisation

Following informed consent and baseline assessment, participants will be randomised using a validated web-based randomisation programme (Sortition) provided by the Oxford Primary Care Clinical Trials Unit (PC-CTU). Women will be allocated to one of the two study groups: self-monitoring or usual care on a 2:1 basis respectively with allocation stratified for recruitment site and parity (0, 1+).

9.5. Blinding and code-breaking

Due to the nature of the intervention it will not be possible to mask the participant, the recruiting clinician or research team. There will be no code breaking procedure as the study is not masked.

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

9.6.1. Description of study intervention(s)

The intervention is daily self-monitoring of blood pressure with weekly urine protein testing, recorded using a multi-component app. Depending on self-monitoring blood pressure readings a 1 step titration in antihypertensive medication may be advised by a clinician, and communicated to the participant via the app.

9.6.2. Description of comparator(s)

The comparator is the usual antenatal care offered.

9.6.3. Description of study procedure(s)

Self-monitoring of blood pressure: Participants in the intervention arm will be provided with a validated monitor for use in pregnancy and pre-eclampsia with instructions for its use. Participants will be asked to measure blood pressure in a seated position with the arm supported on a table or similar so that the cuff is at the level of the heart. They will be asked to measure their BP once daily by taking two readings separated by at least one minute. The second reading should be recorded on the app. Depending on this value, further readings may be requested from the participant.

Training of participants will cover repeating measurements in the case of unusually high or low readings, as well as how and when to seek medical support should they occur. The participant guideline/booklet will provide information about BP and proteinuria testing and give clear advice to women to contact the antenatal care team or other healthcare professional (e.g. General Practitioner (GP)) in the case of maintained high or low BP readings or a positive proteinuria result. The app system will automatically re-state this advice when high or low readings are sent in. Women will continue to be seen as per standard care by their clinical teams (midwives/GPs/obstetricians) throughout regardless of randomisation group.

Those obtaining very high (or very low) BP readings will be given advice to contact their maternity assessment unit within 4 hours. Women not sending BP measurements will receive reminder app messages.

Within the study information it will be made clear that any participant who experiences any symptoms consistent with pre-eclampsia will be advised to contact their maternity assessment unit regardless of their BP reading.

Self-management of anti-hypertensive medication: Raised BP readings with no proteinuria will be reviewed via the app by a suitable healthcare professional. An increase in dose of the participant's usual antihypertensive medication may be recommended by the clinical team, if appropriate, and communicated back to the participant via the app as a message, and by a duplicate SMS. The participant will be asked to confirm the medication they are taking 24h after a medication change. Low BP readings will be reviewed in the same way, and may lead to a recommendation of a reduction in dose of antihypertensive medication. In general, only one remote titration of anti-hypertensive medication can be made between antenatal appointments and assessment by a clinician. If a further titration of antihypertensives is required between antenatal assessments than an in-person clinical review will be organised. (See appendix B)

Self-Proteinuria Testing: Participants in the intervention group will be asked to self-test their own urine weekly. If they have raised BP readings they will then be asked to test their urine more frequently. They will be provided with the necessary kit and guidance on how to do this. If their BP is raised and they have a reading of 1+ or more of urinary protein, then they will be advised to contact their maternity assessment unit. If they have normal BP, but protein in their urine, they may be asked to either repeat the urine test in 24 hours, or contact their maternity assessment unit, depending on the amount of protein detected.

The My Pregnancy Care App:

The app has been developed by the study team at the University of Oxford and the backend servers will be hosted NHS servers, located on the OUH site in Oxford. The developers are researchers from the University and will have access to the anonymised data sets. A limited number of researchers with NHS contracts (Dr. Cristian Roman) will also access the non-anonymised datasets on the NHS servers.

For participating women randomised to the intervention the app will hold information about them including; their name, age and gestation of pregnancy, blood pressure readings, urine testing results, and current medication.

Participants will be notified of dose titrations by a message through the app (and by a duplicate SMS) or by a telephone call from their clinical team. The participant will be asked to confirm the medication they are taking 24h after a medication change.

A participant phone number is needed to send the duplicate blood pressure medication changes message and also the 'password forgot' requests (which occur regularly - participants change phones or delete the App to save space). The database is linked on the NHS server but no identifiable information (first name, last name, phone number) is allowed to be exported from the database. Records are exported and further accessible for research analysis only in pseudo-anonymised format (with the study id). SMS will be used only during registration (to send credentials) and to send new medication plans (or changes). A security assessment was performed for our previous trial, and the current technological stack has not been modified. (BUMP trials REC: 17/WM/0241 and the DAPHNY study, REC: 22/WA/0130).

9.7. Baseline appointment

At baseline an ICF will be signed, then contact details will be recorded; eligibility will be assessed and baseline data (demographics and questionnaires) will be collected prior to randomisation.

Brief medical history, medication history and medical details relevant to pregnancy (such as risk factors for pre-eclampsia) will be recorded.

9.8. Subsequent Visits/Data Collection

Follow up contact 1: questionnaire (by phone call, email, in person or by post (return postage provided)) at around 30 weeks gestation or around 2 weeks after starting the intervention if randomised later than 30 weeks, undertaken by the research team.

Follow up contact 2: questionnaires and collection of the loaned BP monitor (in person, by email, by post (return postage provided) and/or over the phone at around eight weeks following delivery undertaken by the research team. A notes review will be undertaken following the primary discharge for mother and baby. If a woman is still in hospital at 2 months and/or her baby at estimated date of delivery or 2 months (whichever is longer), the admission will be censored and data collected up to that point.

See study flow chart appendix A.

9.9. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw early from the study intervention at any time.

1) Participants may choose to discontinue the intervention or interventions and/or study assessments but may remain on study follow-up.
2) Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely. Data provided up to this point will be retained for use in the study analysis but no further data will be collected.
3) Participants can withdraw completely from the study and withdraw the data collected up until the point of withdrawal. The data already collected would not be used in the final study analysis.

In addition, the Investigator may discontinue a participant from the study 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
- Significant non-compliance with treatment regimen or study requirements
- Clinical decision

If a woman discontinues the intervention, withdraws or is withdrawn from the study at any point, her usual antenatal care will continue as all study procedures are additional rather than in place of usual care.

Participants will not be replaced. The type of withdrawal and reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

9.10. Definition of End of Study

The end of study is the point at which all the study data has been entered and queries resolved.

10. SAFETY REPORTING

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

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

Other ‘important medical events’ may also be considered 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. Causality

The relationship of each adverse event to the trial intervention must be determined by a medically qualified individual according to the following definitions:

- **Unrelated** – where an event is not considered to be related to the intervention.
- **Possibly** – although a relationship to the intervention cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible
- **Probably** – the temporal relationship and absence of a more likely explanation suggest the event could be related to the intervention.
- **Definitely** – the known effects of the intervention, its therapeutics class or based on challenge testing suggest that the intervention is the most likely cause.

All AEs (SAEs) labelled possibly, probably or definitely will be considered as related to the intervention.

10.3. Procedures for Recording Adverse Events

We do not anticipate that the study intervention (self-monitoring of blood pressure, self-testing for proteinuria and remote up-titration of medication) should result in any adverse events (AEs) but include this section in case such events are reported so that they can be considered for causal links to the study. Only AEs that are clinically judged (by the supervising site PI) as being caused by the trial intervention will be reported to the PC-CTU. A serious adverse event (SAE) occurring to a participant will 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.

10.4. Reporting Procedures for Serious Adverse Events

All SAEs occurring during the study, either observed by the recruiting midwife or reported by the participant, whether or not attributed to study intervention, will be recorded and forwarded by the site to PC-CTU, using the relevant report form following assessment for seriousness and relatedness by the site clinician. This form will be completed and sent using secure email, to the PC-CTU using the number/email quoted on the report form. As a minimum, the following information will be recorded:

- Description
- Date of onset
- End date
- Severity
- Assessment of relatedness to study medication
- Other suspect drug or device
- Action taken

Follow-up information should be provided as necessary.

SAEs must be reported to the PC-CTU within 24 hours of discovery or notification of the event. The PC-CTU will acknowledge receipt of the SAE Report Form using the relevant PC-CTU documentation. This receipt will be emailed and faxed to the site physician. If the site physician does not receive a receipt within 24hrs of them sending the report (during office hours), they should re-send the SAE Report Form to the PC-CTU by email or fax and telephone ahead.

The documentation will be reviewed by members of the Trial Management Group and the 'SAE Checklist' will be completed and retained by the PC-CTU. Following the initial check of the report, any additional information will be requested, and the CI or their medically qualified designated representative will review and evaluate the report for seriousness, causality and expectedness. The joint Trial Steering /Data Monitoring Committee (TS/DMC) will agree prospectively how SAE reports will be reviewed.

Additional information, as it becomes available, will also be reported on the paper SAE Report Form (i.e. updating the original form) and returned to the PC-CTU by email or fax as above. The SAE Report Form will be filed in the Trial Master File according to the relevant PC-CTU Standard Operating Procedure (SOP), with copies filed in the woman's notes, the Case Record Form file and the Investigator Site File.

Trial Managers complete regular reports reviewed by the senior members of the PC-CTU. One of the metrics contained within this reporting is the number of SAEs reported and the cumulative number of

SAEs for each study. Any concerns identified will be immediately raised with the CI and may be tabled for discussion at the regular PC-CTU Management Committee meetings or referred to the study's TS/DMC for review. The TS/DMC also monitors the frequency and pattern of events reported as part of its independent oversight of the trial.

A serious adverse event (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, using the HRA report of serious adverse event form (see HRA website).

10.5. Expectedness

We do not anticipate any serious adverse events due to the self-monitoring and proteinuria self-testing intervention.

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 or qualitative work. This will be judged by the CI and medical lead in the acute situation and ratified by the trial and data monitoring committee.

Maternal outcomes including:

- Admission for monitoring or treatment of hypertension or pre-eclampsia
- Systolic BP≥ 150 mmHg (including home monitoring)
- Diastolic BP<70 mmHg
- Need for additional oral or parenteral antihypertensive drugs
- Pre-eclampsia
- Myocardial ischaemia/infarction
- Intubation
- Pulmonary oedema
- Hepatic dysfunction
- Acute kidney injury
- Neurological dysfunction other than stroke (altered Glasgow Coma Scale, blindness, hyperreflexia + clonus, severe headache +hyperreflexia, persistent visual scotoma)
- Disseminated intravascular coagulation
- HELLP syndrome (haemolysis, elevated liver enzymes, low platelets)
- Placental abruption
- Post-partum haemorrhage
- Admission for antepartum haemorrhage, suspected pre-term labour or pre-labour rupture of membranes
- Admission for labour, induction of labour or caesarean section
- Admission for assessment of suspected fetal compromise including poor growth or reduced fetal movements

- Admission for psychiatric or social reasons
- Admission for unstable lie or external cephalic version
- Admission for other pregnancy complications not listed

Although it is known that maternal death and stroke can occur in this group of higher risk women, they will still be reported to the DMC as an SAE.

Perinatal outcomes including:

- Admission to neonatal unit: LDC, HDU, ICU
- Respiratory distress syndrome
- Need for ventilator support
- Intraventricular haemorrhage
- Confirmed infection
- Necrotising enterocolitis
- Seizures
- Encephalopathy
- Other diagnoses related to admission to NNU
- Prematurity and small-for-gestational-age
- Congenital anomalies

Although it is known that stillbirth and neonatal death can occur in this group of higher risk women, they will still be reported to the DMC as an SAE.

11. STATISTICS AND ANALYSIS

A Statistical Analysis Plan (SAP) is to be produced separately and will be finalised before the analysis takes place.

Briefly:

11.1. Description of the Statistical Methods

The analysis will be carried once the final participant has completed follow-up. Continuous variables will be reported as means with standard deviations (or medians with interquartile ranges if data are skewed). Categorical variables will be reported as counts and percentages and categories may be collapsed if there are insufficient data to provide meaningful analysis.

The primary outcome for this feasibility study will be primarily descriptive, presented as proportions and 95% confidence intervals (CIs).

Secondary/exploratory continuous outcomes will be analysed using analysis of covariance and adjusted for stratification factors. Results will be presented as mean differences with 95% CIs.

Further exploratory analysis will look at measures of blood pressure control, including ‘time in range’ for both home and clinic readings, and the amount of antihypertensive medications taken will be compared between the two groups.

Binary outcomes will follow a similar approach using logistic regression models, results reported as relative risk with 95% confidence intervals.

There is no planned interim analysis for this study given that we do not expect any serious adverse events arising from our study procedure statistical analysis plan will be written with our statistical team and will be completed before receipt of the data.

Missing data will be described and explored for associations but will not be imputed.

11.2. Sample Size Determination

No formal sample size calculation is required for this feasibility study. We will aim to recruit 60 women for the randomisation study, across the two sites.

The literature suggests a range of ideal sample sizes for feasibility studies. Julious (2005) recommends 12 in each study arm (16), whereas Teare (2014) suggests that at least 70 subjects (35 per arm) are required to estimate the standard deviation for a continuous outcome when planning onward, larger scale trials (17). As this is not our aim, we will use a smaller total sample size of 60 women. They will be randomised to 40 in the intervention arm and 20 in control arm. This is felt to be realistic given the study population and timescale.

11.3. Analysis populations

The primary analysis population for the feasibility measures will include the whole population and analysed collectively for whom data is available.

Analysis will include all randomised participants meeting the protocol defined eligibility criteria analysed according to the group there were randomised to, regardless of deviation from protocol. (Intention to treat analysis)

Other populations for secondary analysis/exploratory analysis will be defined in the SAP. Participants who withdraw will be included in the analysis until the point of withdrawal.

11.4. Decision points

This feasibility study will not include any interim analysis. Analysis will take place at the end of the study.

11.5. Stopping rules

The trial will stop once recruitment and follow up is complete. The CI will make the final decision to terminate the trial.

11.6. The Level of Statistical Significance

A 95% level of significance will be used.

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

Missing data: Missing data will be reported with reasons given where available and the missing data pattern will be examined. We will explore the mechanism of missing data. The occurrence of missing data is one aspect of the outcome measure of the primary objective of the study.

Spurious data: Spurious data will be assessed using standard editing criteria. The occurrence of spurious data should be limited by the app's data inputting rules (i.e. it will not accept BP readings with a systolic less than 70mmHg or greater than 230mmHg, or diastolic less than 40mmHg or greater than 140mmHg). The participant will be asked to submit the reading again.

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

Any deviation from the original analysis plan will be described in the final report and publications

11.9. Health Economics Analysis

A health economic analysis will not be completed in this feasibility study.

12. DATA MANAGEMENT

The plan for the data management of the study are outlined below. There is not a separate Data Management document in use for the study.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' case report form (CRF, paper and/or electronic) data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), 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, the participant will be referred to by the study participant number/code, not by name.

Data collected from the app includes: BP readings inputted by the participant, urine testing results inputted by the participant, Blood pressure medication changes made.

12.2. Access to Data

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

12.3. Data Recording and Record Keeping

All trial data where feasible will be entered onto electronic CRFs which will link directly to the trial database. This clinical database will be built and managed by the research team and will hold and allow data management of all data points required to conduct the final analysis.

The participants will be identified by a unique trial specific number. The name and any other identifying detail will NOT be included in any trial data electronic file.

We will ensure compliance with the relevant Sponsor organisation's policy.

Data Protection Checklist https://researchsupport.admin.ox.ac.uk/policy/data/checklist
Practical Considerations https://researchsupport.admin.ox.ac.uk/policy/data/practical

13. QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the currently approved protocol, Good Clinical Practice (GCP), relevant regulations and standard operating procedures.

The Trial Management Group (TMG) will be responsible for the monitoring of all aspects of the trial's conduct and progress and will ensure that the protocol is adhered to and that appropriate action is taken to safeguard participants and the quality of the trial itself. The TMG will be comprised of individuals responsible for the trial's day to day management (e.g the CI, trial manager, statistician, data manager) and will meet regularly throughout the course of the trial.

Regular monitoring will be performed according to GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

A joint TSC and DMC will be convened. The precise terms of reference of the joint TSC and DMC, including frequency of meeting, will be agreed by the members.

The joint TSC and DMC will provide overall supervision of the trial and ensure its conduct is in accordance with the principles of GCP and the relevant regulations. The committee will agree the trial protocol and provide advice to the investigators on all aspects of the trial. The committee will include members who are independent of the investigators, in particular, an independent chairperson.

The independent committee will consider the accruing trial and safety data, to ensure trial site staff and participants are aware of any relevant safety information and regarding the appropriateness of continuation of the trial.

13.1. Risk assessment

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2. Study monitoring

There is no planned interim analysis for this study given that we do not expect any serious adverse events arising from our study procedures.

An outcome of pre-eclampsia will be agreed by expert obstetric members from the steering group.

13.3. Joint Trial Steering Committee (TSC) and Data Monitoring Committee (DMC)

The joint TSC & DMC will provide overall supervision of the trial and ensure it is being conducted in accordance with the principles of GCP. The committee will make recommendations about how the trial is operating and review any external relevant evidence that may impact the trial. The committee will also monitor the accruing data to ensure the rights, safety and wellbeing of the trial participants. Composition, roles and responsibilities, and frequency of meetings are detailed in the joint TSC&DMC charter. The committee will advise the trial group about the conduct of the trial based on recruitment data or relevant information external to the trial.

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**.

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, any proposed advertising materials, and questionnaires 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 relating to the study are regarding confidentiality and data protection. Written consent will be sought from the participants for access to their medical records. All members of the research team with access to patient identifiable data will have honorary contracts/letters of access with the relevant NHS Trusts. They will only access the medical records when consent is in place. The number of researchers who need access to patient identifiable information will be kept to a minimum. Any identifiable information recorded for the study will be kept in locked filing cabinets at the University of Oxford or maintained on a secure, restricted, password-protected electronic database.

It is possible that blood pressure monitoring may increase anxiety in participants but previous work by our team has not found this to be common. Participants will be given clear instructions about what to do and who to call if consistently high blood pressure readings are obtained - with the aim of empowering participants and reducing anxiety. If any increase in anti-hypertensive medication is indicated by the home readings, the change in medication communicated will be a pre-agreed step, and will only ever be an increase in a drug they are already taking. They will be able to contact the study team if they have questions. Consideration will be given to the potential sensitivities of pregnant women. We are aware of a need not to worry participants unduly and will consider whether we have achieved this in the qualitative parts of this pilot study. If it becomes apparent during this pilot trial that the questionnaires, information provided or protocol are not acceptable then these will be changed accordingly. Should an individual feel excessively anxious due to study procedures then they will be free to withdraw.

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

To ensure data transparency, the trial will be registered on the International Standard Randomised Controlled Trial Number (ISRCTN) registry before the first participant is recruited.

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 CRF, where participant initials may be added. 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.

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.

17. FINANCE AND INSURANCE

17.1. Funding

The study is funded by the NIHR Applied Research Collaboration (ARC) Oxford and Thames Valley.

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

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the NIHR. Authorship will be determined in accordance with the International committee of Medical Journal Editors guidelines and other contributors will be acknowledged. We will comply with the NIHR open access publishing policy.

At study end, participants will receive a summary of the study's findings and will receive notification of formal publications on request.

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 University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

20. ARCHIVING

All essential documents related to the study, including CRFs, will be archived for at least 5 years after the conclusion of the study, 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 My Pregnancy Care

Invited to participate and provided with information (up to 24 weeks pregnant)

This should take no longer than 5 minutes

Decline

20 week appointment (+/- 4 weeks), extended or with an additional appointment with a member of the research team during which, in addition to standard care:

- The study will be explained
- Informed consent will be taken
- Baseline data obtained

Randomisation

Usual Care group

Self-monitoring

Trained to self-monitor BP, undertake self-management of anti-hypertensive medication following clinical check, self-test for proteinuria; provided with study information; issued with equipment.

30 week follow up contact (visit, phone call or by post)

- Including questionnaires

Postpartum visit or call (around 2 months following delivery 6-10 weeks postpartum):

- Return home monitoring equipment
- Final questionnaires

Notes review (no participant involvement, following primary discharge)

-Clinic recorded blood pressure during pregnancy
-Maternal and perinatal outcomes
-Number of clinical visits
Other secondary outcome data recorded from the antenatal notes

22. APPENDIX B

Blood pressure ranges and actions.

SYS	DIA	What this means	
160+	110+	BP is *very high*	Contact maternity unit within 4 hours
150—159	100—109	BP is ***high***	**Repeat BP reading in 1 hour** **Check urine for protein**
135—149	85—99	BP is *raised*	
100—134	65—84	BP is *normal*	Continue daily monitoring
99 or less	64 or less	BP is *low*	Flag to healthcare team to review medication

23. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.

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