**Trial Title: Blood Pressure Monitoring in high risk pregnancy to improve the detection and monitoring of hypertension**

**Internal Reference Number / Short title:** BUMP RCT

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The authors declare there are no potential conflicts of interest.

**Confidentiality Statement**

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

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## 1. KEY TRIAL CONTACTS

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## 2. SYNOPSIS

| | | |
|---|---|---|
| Trial Title | Blood Pressure Monitoring in Pregnancy to improve the detection and monitoring of hypertension | |
| Internal ref. no. (or short title) | The BUMP studies:<br>BUMP 1: Self-monitoring for the detection of raised blood pressure in pregnancy<br>BUMP 2: Self-monitoring for the management of hypertension in pregnancy | |
| Trial Design | Multicentre randomised controlled trials | |
| Trial Participants | BUMP 1: Pregnant women at higher risk of raised blood pressure<br>BUMP 2: Pregnant women with hypertension<br>Sub-study of women who experience the BPm-Health version of the BUMP app due to COVID-19 changes. | |
| Planned Sample Size | BUMP 1: 2262 (At minimum)<br>BUMP 2: 512 (At minimum)<br>Sub-study of around 30 women who experience the BPm-Health app due to COVID-19 changes | |
| Treatment duration | From recruitment until final follow up (up-to 40 weeks' duration) | |
| Follow up duration | Final follow-up up to 3 months postnatal | |
| Planned Trial Period | 2 ½ years (30 months) | |
| Overall Research Questions | Objectives | Outcome Measures |
| BUMP | To evaluate the use of self-monitoring of blood pressure in pregnancy for the detection and management of hypertension in pregnancy. | Time to raised blood pressure (≥140 and/or 90mmHg) and difference in mean systolic blood pressure, both between groups. |
| **BUMP 1:**<br>Does self-monitoring of blood pressure reduce the time to detection of raised blood pressure in pregnancy compared to usual care? | To evaluate whether self-monitoring of BP can detect raised BP earlier than usual care during pregnancy | Difference in time to recording of raised BP by health care professional between usual care and self-monitoring group. |
| **BUMP 2:**<br>Does self-monitoring of blood pressure to guide management of hypertension in pregnancy lead to better control of blood pressure compared to usual care? | To evaluate whether self-monitoring reduces systolic BP in women with hypertension in pregnancy | Difference in mean systolic BP recorded by health care professionals between usual care and self-monitoring groups. |

# 3. ABBREVIATIONS AND DEFINITIONS

## 3.1. ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| BP | Blood Pressure |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CTRG | Clinical Trials and Research Governance |
| DAU | Day Assessment Unit |
| DMC | Data Monitoring Committee |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| HRA | Health Research Authority |
| ICF | Informed Consent Form |
| ISRCTN | International Standard Randomised Controlled Trial Number |
| ITT | Intention To Treat |
| 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 |
| PIS | Participant Information Sheet |
| PPI | Patient and Public Involvement |
| QALYs | Quality-adjusted life years gained |
| R&D | NHS Trust R&D Department |
| RCT | Randomised Controlled Trial |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| SOP | Standard Operating Procedure |
| TMF | Trial Master File |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |

## 3.2. 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 | Hypertension plus proteinuria and/or multiorgan changes (ISSHP 2012 definition) |
| 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. |

# 4. BACKGROUND AND RATIONALE

## 4.1. What is the problem to be addressed?

Raised blood pressure (BP) affects approximately 10% of pregnancies worldwide, and a high proportion of affected women develop pre-eclampsia. Globally, around 15% of maternal mortality is due to pre-eclampsia so early detection and prevention is paramount. Self-monitoring of BP in pregnancy could improve the detection of gestational hypertensive disorders including pre-eclampsia, whilst also empowering and engaging women in their own care. This study aims to evaluate the use of self-monitoring of BP in pregnancy in women at higher risk of pre-eclampsia for the detection and management of hypertension.

Women who are at higher risk for raised BP in pregnancy (e.g. due to age or previous medical history) require more frequent monitoring.(1) BP can rise rapidly in pregnancy and hypertension may go undetected in between antenatal visits, despite the current extra monitoring in place.(2) Self-monitoring has the potential to allow earlier detection at low cost, reducing maternal morbidity and mortality, whilst at the same time increasing women's involvement in their own care.

Once raised BP is detected, the clinical focus is to treat the BP, monitor for development of pre-eclampsia and to ensure appropriate fetal surveillance.(1) Substantial resources are currently expended in monitoring such women, both from the woman's and the National Health Service' (NHS) perspective. Self-monitoring, if shown to be successful, could both provide more accurate data for clinicians to use for treatment and management strategies and safely reduce the burden of multiple clinic visits for women and midwives.

Self-monitoring of BP, where individuals measure their own BP in a home setting, allows for multiple measurements with little or no disturbance of lifestyle and is now common place in adults with hypertension (3, 4). Self-monitoring has advantages in terms of estimating the underlying BP better than intermittent clinic measurements and, in the context of pregnancy, enabling the detection of raised BP when it happens as opposed to waiting for periodic appointments with a healthcare professional.

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 (5). Although the most recent MBRRACE report showed that deaths associated with hypertension in pregnancy have dropped, pre-eclampsia remains important.(6) Self-monitoring is therefore potentially attractive both for detection and management of hypertension.

## 4.2. Has a systematic review been carried out and what were the findings?

This group has recently completed a systematic review and individual patient data analysis in this area.(7) Studies identified showed that self-monitoring of BP by pregnant women is feasible, popular with participants, and potentially useful in the diagnosis and management of hypertension (8-10). However, these studies included limited monitoring periods with variable regimes, and used monitors not validated for use in pregnancy making it difficult to assess how the clinic readings compares to self-monitored BP. The key findings were:

- Self-monitoring of BP by pregnant women is feasible, popular with participants, and appears potentially useful in the diagnosis and management of hypertension.
- From the data available there appears to be little overall difference between clinic and home monitoring average BP – though there is large variation between studies.
- Only five automated monitors currently on the market are validated for use in pregnancy and only three in pre-eclampsia.

### 4.3. Aims

The overall aims of this trial are to evaluate whether self-monitoring of BP can improve the detection of raised BP during pregnancy and whether self-monitoring can improve the titration of antihypertensive medication in pregnancy hypertension.

### 4.4. How will the results of this study be used?

Self-monitoring of BP in pregnant women has potential to be a successful strategy in the detection of gestational hypertensive disorders that include 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.

### 4.5. Potential Risks

During this randomised controlled 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 BP reading in the self-monitoring and the possibility of increased anxiety due to the study. Training of participants will cover repeated measurements in the case of unusually high or low readings. The participant guideline/booklet will 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 readings. The text/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.

### 4.6. Potential Benefits

Potential benefits for inidividuals taking part include better information about their BP and the possibility that new hypertension will 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.

## 5. OBJECTIVES AND OUTCOME MEASURES

| **Objectives** | **Outcome Measures** | **Time point(s) of evaluation of this outcome measure** (if applicable) |
|---|---|---|
| To evaluate the use of self-monitoring of blood pressure in pregnancy for the detection and management of hypertension in pregnancy. | Time to raised blood pressure (≥140 and /or 90mmHg) and difference in mean systolic blood pressure, both between groups. | Notes review (completed following primary discharge) |
| **BUMP 1: Primary Objective**<br>To evaluate whether self-monitoring of BP can detect raised BP earlier than usual care during pregnancy | Difference in time to recording of raised BP by health care professional between usual care and self-monitoring group. | Notes review (completed following primary discharge) |
| **BUMP 1: Secondary objectives**<br>To evaluate the effect of self-monitoring in higher risk pregnancy on maternal and perinatal adverse outcomes.<br><br>To evaluate whether self-monitoring of blood pressure in higher risk pregnancy affects quality of life and is cost-effective?<br><br>To evaluate how self-monitoring of blood pressure in higher risk pregnancy is implemented in daily life and routine clinical practice? | **Maternal**<br>Difference between usual care and self-monitoring group in:<br>• Severe hypertension (systolic BP ≥160mmHg and/or or diastolic BP ≥110mmHg)<br>• Serious maternal complications (pre-eclampsia, placental abruption, transient ischemic attack or stroke, pulmonary oedema, renal failure, blood transfusion), death<br>• Onset of labour<br>• Quality of life: EQ-5D-5L<br><br>**Perinatal**<br>• Stillbirth<br>• Early neonatal deaths<br>• Gestation at delivery<br>• Mode of delivery<br>• Birth weight including centile<br>• Small for gestational age infants (<10th and <3rd centile)<br>• Neonatal unit admissions including length of stay<br><br>**Process**<br>• Health Behaviours<br>• Fidelity to monitoring schedule<br>• STAI-6 short form anxiety questionnaire<br>• Health service costs: outpatient consultations (primary & secondary care), inpatient stays, type and dose of antihypertensive medication.<br>• Cost per quality-adjusted life year gained over trial period. | Notes review (which will take place following primary discharge) except: EQ-5D-5L, STAI and health behaviour questions which will be asked at baseline and follow up (at around 30 weeks and 8 weeks postpartum). |

| | | |
|---|---|---|
| | **Qualitative**<br>• Experiences of women and healthcare professionals of their involvement in the trial<br>• Understanding of why some women chose not to participate in the trial<br>• Social network mapping with interviews and questionnaire.<br>• Views of women and healthcare professionals around the subject of self-management<br>• Views of HCPs on the integration and implementation new technologies and complex interventions in health care | |
| **BUMP 2: Primary Objective**<br>To evaluate whether self-monitoring reduces systolic BP in women with hypertension in pregnancy | Difference in mean systolic BP recorded by health care professionals between usual care and self-monitoring groups. | Notes review (completed following primary discharge) |
| **BUMP 2: Secondary objectives**<br>To evaluate the effect of self-monitoring of BP on other measures of BP in hypertension in pregnancy<br><br>To evaluate the effect of self-monitoring in hypertension in pregnancy on maternal and perinatal adverse outcomes.<br><br>To evaluate whether self-monitoring of blood pressure in hypertension in | **Maternal**<br>• Difference in mean diastolic BP between usual care and self-monitoring groups.<br>• Difference in the mean area under the BP over time curve between usual care and self-monitoring group.<br>• Difference in the mean proportion of readings above 140mmHg (BP load) between usual care and self-monitoring group.<br>• Severe hypertension (systolic BP ≥160 or diastolic BP ≥110mmHg)<br>• Serious maternal complications (pre-eclampsia, placental abruption, transient ischemic attack or stroke, pulmonary oedema, renal failure, blood transfusion), death.<br>• Onset of labour<br>• Quality of life: EQ-5D-5L<br><br>**Perinatal**<br>• Gestation at delivery<br>• Birth weight including centile<br>• Small for gestational age infants (<10th and <3rd centile)<br>• Neonatal admissions including length of stay<br>• Stillbirth | Notes review (completed following primary discharge) except: EQ-5D-5L, STAI and health behaviour questions which will be asked at baseline and follow up (at around 30 weeks/2 weeks following randomisation and 8 weeks postpartum). |

| | | |
|---|---|---|
| pregnancy affects quality of life and is cost-effective?<br><br>To evaluate how self-monitoring of blood pressure in hypertension in pregnancy is implemented in daily life and routine clinical practice? | • Early neonatal deaths<br>• Mode of delivery<br><br>**Process**<br>• Health Behaviours<br>• Fidelity to monitoring schedule<br>• Adherence to medication: MARS questionnaire<br>• STAI-6 short form anxiety questionnaire<br>• Health service costs: outpatient consultations (primary & secondary care), inpatient stays, type and dose of antihypertensive medication.<br>• Cost per quality-adjusted life year gained over trial period.<br>**Qualitative**<br>• Experiences of women and healthcare professionals of their involvement in the trial<br>• Understanding of why some women chose not to participate in the trial<br>• Social network mapping with interviews and questionnaire.<br>• Views of women and healthcare professionals around the subject of self-management<br>• Views of HCPs on the integration and implementation new technologies and complex interventions in health care<br>• Experiences of women of their experiences of self-monitoring of BP brought in following changes to reduce face to face contact during COVID-19 pandemic. | |

## 6. TRIAL DESIGN

This study is a non-masked RCT of self-monitoring of BP during pregnancy. The work is part of a larger programme of work investigating the use of self-monitoring and testing during pregnancy.

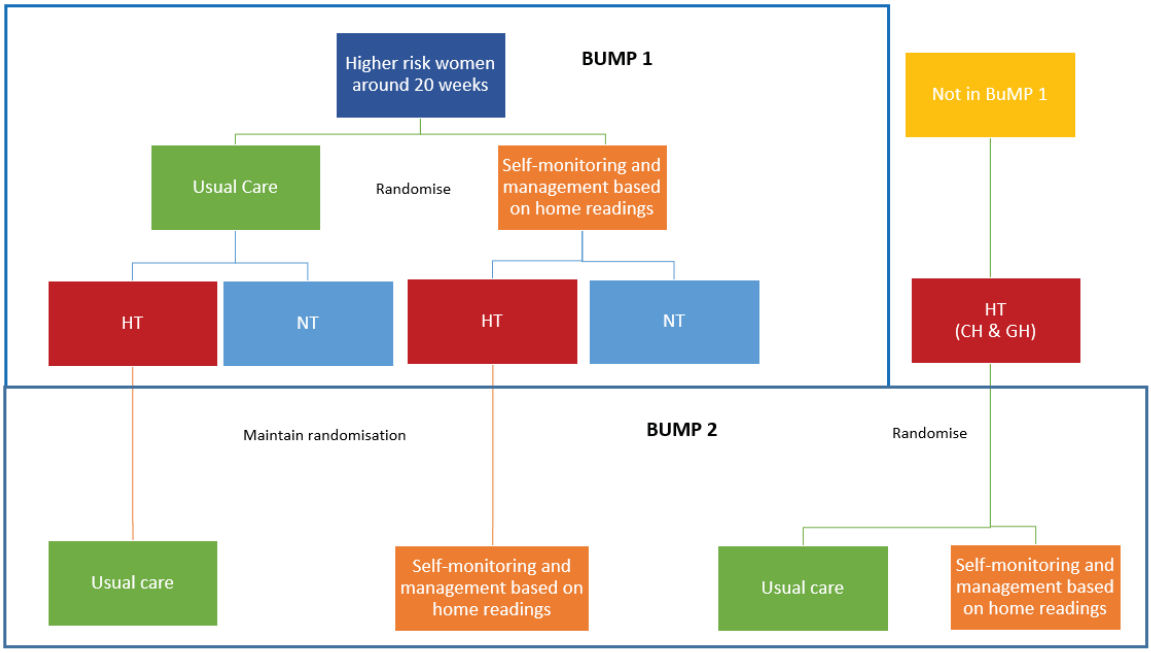
**BUMP 1**: BUMP 1 will be a prospective non-masked RCT of self-monitoring of BP in pregnancy for the detection of raised BP. Recruitment will be through antenatal care predominantly in secondary care. Women will be invited to participate if they are defined as at higher risk of pre-eclampsia (see inclusion criteria). The consent process for BUMP 1 will include discussion of procedures should a woman develop pregnancy hypertension and explain the seamless transition into BUMP 2.

**BUMP 2**: BUMP 2 will be an RCT of self-monitoring of BP for the management of hypertension in pregnancy in women with chronic hypertension or gestational hypertension. Women may enter this study from BUMP

1 (maintaining original randomisation) or be recruited with chronic or gestational hypertension without prior involvement in BUMP 1.

There will be an external pilot phase including up to 50 women in order to test trial procedures prior to full recruitment.

**Figure 1. Study design**




HT – hypertension, NT – normotension, CH chronic hypertension, GH – gestational hypertension

# 7. BUMP 1: Methods

## 7.1. PARTICIPANT IDENTIFICATION

### 7.1.1. Trial Participants

Pregnant women at higher risk of pre-eclampsia (as defined by risk factors identified in the NICE guidelines) will be invited to take part. (11)

### 7.1.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the trial
- Pregnant woman, aged 18 years or above between 16+0 to 24+0 weeks
- Able and willing to comply with trial requirements
- Willing to allow her GP and consultant, if appropriate, to be notified of participation in the trial
- At higher risk for hypertension in pregnancy / pre-eclampsia defined as one or more of the following risk factors:
  - Age 40 years or older
  - Nulliparity
  - Pregnancy interval of more than 10 years
  - Family history of pre-eclampsia
  - Previous history of pre-eclampsia or gestational hypertension
  - Body mass index 30 kg/$m^2$ or above at booking
  - Chronic kidney disease
  - Twin pregnancy
  - Diabetes (Type 1&2)
  - Autoimmune Disease (eg systemic lupus erythematosis or antiphospholipid disease)

### 7.1.3. Exclusion Criteria

- Chronic hypertension

## 7.2. TRIAL PROCEDURES

### 7.2.1. External Pilot

In order to test trial procedures, in particular recruitment randomisation and the “real time” use of the telemonitoring system, an external pilot in one site will be undertaken. This will aim to use identical procedures to the main trial as outlined below.

### 7.2.2. Recruitment

Health care professionals will screen notes for women who are likely to be eligible for the trial. These women will be approached and provided with study information. Women interested in taking part will be offered a study visit (alongside standard antenatal care appointments where possible) at around 16-24 weeks’ gestation. Potential participants will be provided with study information at any time from early pregnancy (at their first antenatal care visit) up until 24 weeks. Women interested in taking part

will be invited to attend a study visit at around 20 weeks (+/-4 weeks) with a midwife, 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.

Potential participants will be given opportunity to ask questions about the study. If they are willing to take part, the research midwife will take informed consent. 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.

### 7.2.3. 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 records of potentially eligible women to assess eligibility who will provide a patient information leaflet to interested women, and 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.

### 7.2.4. Informed Consent

Written versions of the Participant Information Sheet (PIS) and Informed Consent Form (ICF) will be presented to the participants.

The person taking informed consent for women in BUMP 1 will explain that should they develop hypertension in pregnancy, they will continue in their randomisation group and move into BUMP 2, with seamless transition. At any time, women will be free to discontinue the intervention or withdraw from the trial for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give a reason for withdrawal.

Women will be allowed as much time as they wish, up to 24 weeks gestation, to consider the trial information, and the opportunity to question the person delegated to take consent, their GP or other independent parties to decide whether they will participate in the trial. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the ICF. The person who obtains the consent must be suitably qualified, experienced and GCP trained and delegated the responsibility on the Site Signature Delegation log. Once copy of the signed ICF will be given to the participant; one copy will be stored in the notes; one copy will be sent to the PC-CTU.

Women can be approached up to 24 weeks gestation to be part of the study. If a woman wishes to take part in the study on the same day that they receive information, given the low risk nature of the study, they may be consented and have their baseline visit on the same day as they are approached. The woman can subsequently withdraw consent at any point in the study without penalty having taken more time to consider participation. Women wishing longer to consider participation will be offered such.

### 7.2.5. Randomisation, blinding and code-breaking

A secure web-based randomisation system will be 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 1:1 basis respectively with allocation stratified for recruitment site and parity.

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.

### 7.2.6. Baseline Assessments

ICF will be signed; contact details will be recorded; eligibility will be assessed and baseline data from the questionnaires will be collected prior to randomisation.

Women randomised to self-monitoring will be provided with a validated monitor for use in pregnancy and pre-eclampsia and instructions for its use. They will be signed up to the text/app system and provided with instructions.

### 7.2.7. Subsequent Contacts

Women will remain in the study until the final follow-up contact, or entry into the BUMP 2 study.

**Follow up contact 1:** questionnaire (by phone call, email, in person or by post) at around 30 weeks' gestation 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) around eight weeks after birth 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 1.

### 7.2.8. Discontinuation/Withdrawal of Participants from Trial Treatment/Crossover

Each participant has the right to discontinue the intervention or withdraw from the trial at any time. In addition, an Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- An adverse event which results in inability to continue to comply with trial procedures
- Withdrawal of Consent
- Loss to follow up

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.

Women who wish to discontinue the BP self-monitoring intervention will be asked if they are willing to participate in study follow-up. All data collected to the point of withdrawal will be retained in the study database. Unless a participant specifically withdraws consent, notes review will be conducted, even where an individual has been lost to follow-up.

Women randomised to usual care will not be prevented from self-monitoring although we will ask their clinicians to base their management on clinic blood pressure. We will ask all women at final follow-up if they have self-monitored during the trial.

### 7.3. Definition of End of Trial

The end of trial is the last data capture after the last participant's last visit/discharge/date of censor.

### 7.4. Usual care

Women randomised to usual care will receive standard antenatal care as practised in the participating site. Should a woman randomised to usual care develop pregnancy hypertension, there will be no additional intervention and they will receive standard antenatal care as appropriate for a woman with pregnancy hypertension. They will move seamlessly into BUMP 2 (see below) for the purposes of subsequent data capture.

### 7.5. Intervention

In addition to usual care, women randomised to the intervention will be asked to measure their BP on at least three days a week, using the standard procedure, once daily at the same time of their choosing. Two readings will be taken and the second reading recorded and acted upon if necessary.

Women will be asked to send their BP reading to an app/text. Women obtaining a second reading that is out-of-range BP readings will be asked to do a third measurement. If their third measurement is out of range, women will be advised to contact their midwife, GP or their local maternity Assessment Unit. Women not sending BP measurements will receive reminder texts/app messages.

Women having any symptoms consistent with pre-eclampsia will be advised to contact their maternity unit for assessment regardless of their BP reading. The accompanying information booklet includes information around understandings of pre-eclampsia and the importance of awareness and detection of any of suggestive symptoms.

Clinicians will be asked to use self-monitored blood pressure to guide their management. Thresholds are based on current NICE guidance, ie 140/90mmHg, in terms of the alerts women will receive although clinicians will be free to choose the threshold blood pressure that they use provided it is not different between intervention and control.

Participants and clinicians will be provided with a Freephone number to use in case of any study-related queries, otherwise women will continue to contact their maternity units (and/or GPs/midwives) for any clinical queries via the usual route detailed in their maternity notes.

In the case of the development of pregnancy hypertension for women randomised to self-monitoring, they will receive standard antenatal care as appropriate for a woman with pregnancy hypertension and the frequency of self-monitoring recommended will increase to daily as their BP rises and once

hypertensive their self-monitored BP will be used to guide ongoing management. They will move seamlessly into BUMP 2 (see below).

### 7.6. Adherence to Trial Intervention

Weekly motivational messages will be sent to women in the intervention group via the app or text system based on the women's preference. These will be selected at random from a pool of messages.

### 7.7. Post-Trial

Self-monitoring of BP will finish at admission in established labour or the end of pregnancy, whichever is sooner. The monitors will be returned to the study team either at delivery or at the final follow up assessment (8 weeks postpartum).

## 8. BUMP 2: Methods

### 8.1. PARTICIPANT IDENTIFICATION

#### 8.1.1. Trial Participants

Two separate groups of women will be eligible: i) women in BUMP 1 that develop raised BP and ii) pregnant women with hypertension not in BUMP 1

#### 8.1.2. Inclusion Criteria

The study population will comprise of pregnant women with hypertension:

- Women developing pregnancy hypertension previously randomised in BUMP 1 (regardless of gestation).

OR

- Women with **chronic hypertension** (defined as sustained systolic BP≥140 mmHg and/or diastolic BP≥90 mmHg, present at booking or before 20 weeks' gestation, or receiving treatment outside pregnancy and/or at time of referral).
- Recruited up to 37+0 weeks' gestation.

OR

- Women with **hypertension** after 20 weeks' gestation (defined as sustained systolic BP≥140 mmHg and/or diastolic BP≥90 mmHg).
- Recruited at 20+0 to 37+0 weeks' gestation.

- Participant is willing and able to give informed consent for participation in the trial.
- Woman aged 18 years or above.
- Willing to allow her GP and consultant, if appropriate, to be notified of participation in the trial.

#### 8.1.3. Exclusion Criteria

The participant may not enter the trial if the following applies:

- Anticipated inpatient admission considered likely to lead to imminent delivery (within the next 48 hours)

## 8.2. TRIAL PROCEDURES

#### 8.2.1. External Pilot

In order to test trial procedures, in particular recruitment randomisation and the "real time" use of the telemonitoring system, an external pilot in one site will be undertaken. This will aim to use identical procedures to the main trial as outlined below.

#### 8.2.2. Recruitment

Women previously consented into BUMP 1 will move seamlessly into BUMP 2 without needing further consent. This is because the consent procedure including patient information for BUMP 1 includes information regarding the trial should a participant develop hypertension.

For women not previously randomised into BUMP 1, research midwives and/or clinical staff will screen notes for women who are likely to be eligible for the trial. These women will be approached and provided with study information. Verbal consent will be gained to pass on details to the research team. Women interested in taking part will be offered a study visit (alongside standard antenatal care appointments where possible) at which they will be able to ask questions about the study. Potential participants with chronic hypertension will be provided with study information at any time from early pregnancy (at their first clinic visit) up until 37 weeks. Women with a diagnosis of gestational hypertension not previously randomised into BUMP 1 will be provided with study information anytime from first diagnosis until 37 weeks. Women interested in taking part will be invited to attend a study visit with a research midwife. If they are willing to take part the research midwife will take informed consent. Once a participant has consented to take part in the study, baseline information and questionnaires will be recorded. The participant will then be randomised to control or intervention groups.

#### 8.2.3. Screening and Eligibility Assessment

For women not previously randomised into BUMP 1, screening and randomisation may take place within the same study visit. Health care professionals will screen the records of potentially eligible women to assess eligibility who will provide a patient information leaflet to interested women, and 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 8.1.2 and 8.1.3. Women randomised into BUMP 1 will maintain their randomisation group and their study ID.

### 8.2.4. Informed Consent

For women not previously randomised into BUMP 1, written versions of the PIS and ICF will be presented to potential participants. It will be clearly stated that the participant is free to discontinue the intervention or withdraw from the trial 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 wished 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 trial. Written informed consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the ICF. The person who obtained the consent must be suitably qualified and experienced, experienced and GCP trained and delegated the responsibility on the Site Signature Delegation log. Once copy of the signed ICF will be given to the participant; one copy will be stored in the notes; one copy will be sent to the PC-CTU.

If a woman wishes to take part in the study on the same day that they receive information, given the low risk nature of the study, they may be consented and have their baseline visit on the same day as they are approached. The woman can subsequently withdraw consent at any point in the study without penalty having taken more time to consider participation. Women wishing longer to consider participation will be offered such.

### 8.2.5. Randomisation, blinding and code-breaking

Women taking part in BUMP 1 who develop hypertension and are eligible for BUMP 2 will continue in the group they were originally randomised to. Women not previously participating in BUMP 1 will be allocated to one of the two study groups: self-monitoring or usual care on a 1:1 basis respectively with allocation stratified for recruitment site and parity. A secure web-based randomization system will be provided by the PC-CTU.

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.

All women in both arms of the study will continue to receive standard antenatal care as appropriate for a woman with pregnancy hypertension.

### 8.2.6. Baseline Assessments

For women not previously randomised into BUMP 1, an ICF will be signed; contact details will be recorded; eligibility will be assessed and baseline data will be collected (demographics and questionnaires).

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

### 8.2.7. Subsequent contacts

**Follow up contact 1:** questionnaire (by phone call, email, in person or by post) 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 2.

### 8.2.8. Discontinuation/Withdrawal of Participants from Trial Treatment/Crossover

Each participant has the right to discontinue the intervention or withdraw from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- An adverse event which results in inability to continue to comply with trial procedures
- Withdrawal of Consent
- Loss to follow up

Women who wish to discontinue the BP self-monitoring intervention will be asked if they are prepared to participate in study follow-up. Previously recorded study data will be maintained. Unless a participant withdraws consent, notes reviews will be conducted, even where an individual has been lost to follow-up.

Women randomised to usual care will not be prevented from self-monitoring although we will ask their clinicians to base their management on clinic blood pressure. We will ask all women at final follow-up if they have self-monitored during the trial.

## 8.3. Definition of End of Trial

The end of trial is the last data capture after the last participants' last visit/discharge/date of censor.

## 8.4. INTERVENTION: Self-Monitoring of BP

Women participating in BUMP 1 will move seamlessly into BUMP 2. As their BP rises, they will receive advice to increase their BP monitoring to daily.

Participants not previously participating in BUMP and randomised to self-monitoring will be provided with a validated monitor for use in pregnancy and pre-eclampsia and instructions for its use. They will be asked to measure their BP daily, using the standard procedure, once daily at the same time of their choosing. Two readings separated by at least one minute should be taken and the second reading recorded and acted upon if necessary.

Women will be asked to send their BP reading via an app/text. Women obtaining repeated out-of-range BP readings will be automatically advised to contact their midwife, GP or local maternity Assessment Unit. Women not sending BP measurements will receive reminder texts/app messages.

Women having any symptoms consistent with pre-eclampsia will be advised to contact their maternity unit for assessment regardless of their BP reading.

Clinicians will be asked to use self-monitored blood pressure to guide their management. Thresholds are based on current NICE guidance, ie Target of 140/90mmHg, in terms of the alerts women will receive although clinicians will be free to choose the target blood pressure that they use provided it is not different between intervention and control.

Participants and clinicians will be provided with a Freephone number to use in case of any study-related queries, otherwise it is expected for clinical queries women will contact their maternity units/midwives/GP via the usual route detailed in their maternity notes.

### 8.5. Adherence with Intervention

Weekly motivational messages will be sent to women in the intervention group via the app or text system. These will be selected at random from a pool of messages.

### 8.6. Post Trial

Self-monitoring of BP will finish at delivery or end of pregnancy or when a woman decides to stop monitoring, whichever is sooner. The monitors will be returned to the study team at the final follow up assessment.

## 9. Qualitative Sub-Studies

These sub-studies will aim to understand how BP self-monitoring in pregnancy is implemented and acceptable in daily life and routine clinical practice and will potentially involve both women in BUMP 1 and BUMP 2 as well as HCPs involved in their care. Any woman who has experience of home monitoring or using the BUMP (including BPm-Health version) app may be asked to share her views, [in particular those asked to home monitor as a result of the COVID-19 pandemic.]

The qualitative research will focus on four different points of interest, designed as four qualitative sub-studies**.** The first sub-study will be an ethnographic study involving in-depth interviews with a sample of participating women and healthcare professionals with experience of the trial. The second sub-study will investigate the social support network of participants and map these interactions using interviews and questionnaires. The third sub-study will look in to the possibility of patient's self-managing their own BP and testing their own proteinuria during pregnancy from the perspective of pregnant women and healthcare professionals. The fourth sub-study will focus on the implementation of the intervention using a survey of all healthcare professionals at participating sites who may have encountered women self-monitoring their BP at home for the trial. The first three sub-studies will seek to talk to participating women, the first sub-study will also seek to talk to some women who decline to take part and QSS-1, 3 and 4 will involve HCPs.

As a result of the COVID-19 pandemic, remote consultations, including home BP monitoring, are being brought into place across UK antenatal clinics (from late March 2020). Some women taking part in this remote monitoring will be asked to share their views and experiences of home monitoring [in telephone or online interviews and/or on postcards] to support sub-study four, which examines implementation of home monitoring.

A description of the optional sub-studies and interviews will be provided to women and healthcare professionals at the point of enrolment in the form of a separate specific PIS. A sample of women who have consented to contact at main trial enrolment will be contacted by a qualitative researcher through phone/SMS/email/in person regarding the interviews and provided with an opportunity to ask questions at this time. Women undertaking home monitoring as a result of the COVID-19 pandemic will be approached by their usual care team or research midwives who will inform them about the study, provide a PIS about the study and ask if they would be willing to be contacted by a qualitative researcher [remotely]. Women will be approached alongside their usual care during pregnancy. No information will be collected from their medical notes.

**Qualitative Sub-Study 1: Ethnographic study**

Qualitative data will form an important part of the process evaluation of the trial, to develop an understanding of the impact and acceptability of self-monitoring. The aim of the qualitative work is to understand how BP self-monitoring in pregnancy is enacted and integrated into women's lives and into routine clinical practice, and where facilitators and barriers to successful implementation lie.

1. *Ethnographic Observations*

A sample of approximately 10-15 women who monitor their BP will be recruited to take part in longitudinal interviewing and non-participatory ethnographic observations to understand the day-to-day operation of the trial procedures in detail. Following participant consent, women's experiences of monitoring and interacting with clinicians will be observed at intervals between 20 weeks' gestation and delivery. This will include: a point of entry interview (incorporating at-home observation of self-monitoring practices using 'think aloud' techniques), accompanying women to two regular appointments for observation, and a final exit interview (the postnatal interview conducted with the wider sample, see below).(12, 13) We have experience of using these methods successfully in other studies; the ethnographic observations will provide detailed insight into how the intervention plays out in practice to inform overall trial results. Both our patient and professional advisors believe personal observation would be acceptable and not unduly onerous, particularly as we are looking for a relatively small sample. Similar techniques have worked well in our feasibility studies. This qualitative work will build on the qualitative interviews conducted with a small sample of women who participated in the BUMP pilot work (16) and intervention development work conducted in the introductory work prior to this trial. If women and/or professionals prefer, consultations will be audio or video-recorded without a researcher present.

2. *Interviews with participating women*

We will aim to include interviews with around 40 women (separate from the observations) across the sites, including a sample of up to eight women who decide not to take part or withdraw and are willing to be interviewed. This will give us a diverse sample to help us understand real-life implementation issues with self-monitoring of BP and experiences of transitioning from BUMP 1 to BUMP 2 (i.e. of becoming hypertensive in BUMP1, see figure 1). 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. Women who experience raised home BP readings will

be purposively sampled to explore their feelings, experiences of subsequent care and how they felt health professionals responded to the home readings. The semi-structured interviews will be conducted in their own homes, over the telephone, or at one of the study sites if preferred. The timing of the interviews will be at various time points during pregnancy and up to 12 weeks postnatally allowing flexibility around the woman's preferences. Interviews will last approximately 30-60 minutes and will be audio-recorded for transcription and analysis.

*3. Semi-structured interviews with healthcare professionals*

Interviews will be conducted with 30-40 midwives and obstetricians involved in the study (up to 10 from any single hub). These will build on the focus group findings from the intervention development work and aim to understand how self-monitoring was operationalised in practice and provide key information for the process evaluation. Anticipated issues will include whether healthcare professionals found the home readings helpful, if they were utilised in a woman's care, how they influenced the diagnosis of pregnancy hypertension, how divergent home and clinic results were interpreted, whether further confirmatory tests were required (e.g. ambulatory monitoring), and whether they felt their professional clinical judgement was encroached upon.

*4. Analysis*

Detailed field notes will be taken of observations and observed appointments will be recorded so that content can be transcribed. The interviews will be audio-recorded and transcribed. Transcripts and field notes will be coded in NVivo and analysed thematically. Data collection and analysis will be informed by theory, drawing on both the concepts of social cognitive theory ,(14) and normalisation process theory (NPT) constructs as an interpretative framework to understand how the trial intervention 'fits' within existing practices and systems, and how it becomes embedded (or not) in both women's and healthcare professionals' routine work.(12, 13)

**Qualitative Sub-Study 2: Social network mapping**

A mixed methods study with participating women will explore the sources of support within personal networks and how this is integrated with their healthcare experience and participation in the trial. This will be done through network mapping and in depth interviews with participating women to explore the sources of support within their personal networks and how this is integrated with their healthcare experience and participation in the trial. A sample of 25-30 women will be purposively sampled. Women will be invited to take part in three assessments to take place; on entry to the study, at approximately 36 weeks gestation and postnatally (approx. 12 weeks after birth). Women will receive a £10 voucher for each of the three visits (max £30 of vouchers) as reimbursement for their time.

*1. Network mapping:*

Generating Engagement in Network Involvement (GENIE) is a facilitated web-based social networking tool (www.genie.soton.ac.uk). Using the concentric circles method (22), participants are guided through the process of thinking of (and consequently mapping) the relationships relevant to health and wellness (which may include family members, friends, acquaintances, healthcare professionals, local groups and online information/ support) (22-24). Previous work has highlighted that this process realigns thinking (i.e. conceptualisation of self as the centre of the network), enables participants to explore family dynamics and recognise the role of others in the network (22). The GENIE mapping tool will be used to

create a visual image of a participant's personal support network, with each of the 3 circles representing degrees of importance in terms of support. For each network member additional information will be collected about the type of relationship, frequency of contact and may look at connections between network members (to examine network density). The mapping exercise will be done online.

1. *Questionnaires:*

At each assessment women will be asked to complete a brief set of questionnaire measures. These will comprise:

- Collective efficacy (CENS) – 12 items measuring network responsiveness and access to collective efficacy.
- Loneliness (De Jong Scale) – 6 items measuring social loneliness and emotional loneliness.
- Relationship quality (revised dyadic adjustment scale) – 14 items measuring couple consensus, satisfaction and cohesion.

Behavioural data will also be collected within the main RCT and includes self-efficacy and anxiety (which will be collected at 30 weeks' gestation and up to 12 weeks postnatally).

2. *Qualitative interviews with participating women:*

These semi-structured interviews will focus on the types of support that are important to women during their pregnancy, and how support networks are integrated, particularly in the context of blood pressure self-monitoring and the healthcare experience in pregnancy. We will also explore the way in which participation in the intervention (implementing self-monitoring into pregnancy) interacts with the personal social network, particularly in relation to the role of healthcare professionals.

3. *Analysis*

The network mapping data will be used to distinguish between types of networks and network properties associated with self-management support [22, 23].We will analyse the extent and nature of contacts within the social network, how new sources of information or support are identified and integrated into the network, including how new connections improve capacity to enact health behaviours, improve wellbeing or reduce isolation. Comparisons will be made across time points, to explore changes in circumstances (such as use of health care services) [24].

All interviews will be audio-recorded and transcribed. A thematic analysis of interview data will be conducted to ensure an inductive approach. Repeated readings of transcripts and listening of recordings will assist familiarisation with the data and identification of initial codes, these will then be defined and guide analysis of the full data set. Using constant comparison, a technique derived from grounded theory transcripts will be compared within and between each other aiding the iterative search for themes, which will then be reviewed, defined and named.

Quantitative data will be used to undertake exploratory statistical analysis to examine relationships between network composition and collective efficacy, relationship adjustment and loneliness. These associations will be assessed using bivariate correlations, with linear regression modelling to predict outcomes (if appropriate).

**Qualitative Sub-Study 3: Enabling self-management**

We wish to explore the possibility of self-management of BP during pregnancy alongside self-monitoring

of BP and self-testing for proteinuria, with pregnant women and their health care professionals.

1. *Focus groups and detailed interviews with antenatal care staff*

We will conduct focus groups (n=4-8) and interviews (n=7-15) with a range of antenatal health care professionals about their attitudes to, and experiences of, self-management to identify any barriers to implementation. Healthcare professionals will be approached by the research team. The semi-structured interviews will be conducted in their own homes, over the telephone, or at one of the study sites if preferred. A topic prompt guide informed by our work in this area will be used. Interviews will last around 15-30 min and will be audio-recorded for transcription and analysis. Focus groups of around 3-5 participants are likely to be held at hospital sites for the convenience of staff, they are expected to last around 30-45 min and will be audio-recorded.

2. *Survey of antenatal care staff*

A detailed survey of 100 obstetric clinicians, in a range of settings, will allow us to understand the frequency of monitoring and level of self-management that would be acceptable during pregnancy. The survey will include free text sections so that health care professionals can explain their views. We anticipate a 30-50% response rate and plan to approach around 250 clinical staff.

3. *Focus groups and Development work with pregnant women*

Focus groups with pregnant women (6-8 groups of around 3-5 women), will explore women's attitudes towards self-monitoring of BP, self-titration of medication, proteinuria testing during pregnancy, and the patient groups most likely to benefit. Women will be approached by the research team who will provide study information. Focus groups will last around 30-45 min and will be arranged at locations convenient to women.

4. *Analysis*

Descriptive statistics will be used to present survey data, including 95% confidence intervals by standard methods. The interviews and focus groups will be audio-recorded and transcribed. Transcripts and free text responses will be separately coded in NVivo and will be separately analysed thematically using the modified Framework approach and NVivo software. Provisional analytic categories will be iteratively refined using the constant comparative method as new data emerge with continued interviewing. The person-based approach to planning and development will be used, coupled with a theory- and evidence-, to identify the key behavioural techniques to be used in the context of the intervention.

**Qualitative Sub-Study 4: Implementation Survey of HCPs and interviews with women**

The aim of this sub-study is to assess implementation processes from the perspective of HCPs whose work may be affected by the BUMP intervention or who have encountered women self-monitoring their blood pressure as part of COVID-19 related changes to management. Women with experience of self-monitoring due to the COVID-19 pandemic will also be interviewed (remotely). This will be part of a mixed methods approach, complementing the qualitative interviews which also aim to understand the barriers and facilitators of implementing the intervention using normalisation process theory (NPT). (12,13)

NPT concerns understanding the complexity of the work involved in implementation and proposes four constructs that represent different kinds of work that people do around implementing a new practice: Coherence, Cognitive Participation, Collective Action, and Reflexive Monitoring. Specifically, NPT is concerned with identifying and understanding the ways that people make sense of the work of

implementing and integrating a complex intervention (coherence); how they engage with it (cognitive participation); enact it (collective action); and appraise its effects (reflexive monitoring).

1. *Survey of HCPs*

All HCPs) who encounter pregnant women self-monitoring their blood pressure will be eligible to complete a brief questionnaire. This will complement the interviews and also follow on from the focus group findings from the intervention development work. The purpose of utilising an additional survey approach is to provide a more complete picture of the views of all staff involved in and affected by pregnant women self-monitoring.

The NoMAD instrument is constructed specifically to relate to the four constructs of NPT. It can be used to describe participants' views about how an intervention impacts on their work, and their expectations about whether it could become a routine part of their work. It can also be used as a way of improving implementation by identifying areas needing further work to progress an implementation project. For example, responses may indicate that the intervention 'makes sense' to participants (Coherence), but that specific aspects of engagement (Cognitive Participation) appear low, suggesting further effort could be targeted at broadening participation or working on participants' commitment to making the intervention work.

*Paper Survey:* The cross-sectional survey will be administered to all consenting HCPs who encounter pregnant women self-monitoring their blood pressure as a result of either their participation in the BUMP trial (up to 200 HCPs) or due to changes in monitoring approaches caused by the COVID-19 pandemic. The survey will be provided in paper format. The survey will take around 15 minutes to complete and participants will only complete it once.

*Online Survey:* Due to the COVID-19 pandemic it is not currently feasible to distribute and collect paper surveys. A reduced online version of questionnaire will be available consisting of less questions and with the exclusion of less sensitive data collection. The online survey will be available to all HCPs who encounter the self-monitor of blood pressure whether they have participated in the BUMP trial. The online survey will take around 5 minutes to complete and participants will only complete it once.

Due to the nature of the online questionnaire full informed consent will not be collected and instead an online agreement will be selected by those completing the survey.

2. *Analysis*

Descriptive statistics will be used to present survey data, including 95% confidence intervals by standard methods.

3. *Interviews with women with experience of self-monitoring due to the COVID-19 pandemic*

Some women taking part in remote monitoring due to the COVID-19 pandemic will be asked to share their views and experiences of home monitoring [in telephone or online interviews and/or on postcards] to support this sub-study examining implementation.

Women undertaking home monitoring as a result of the COVID-19 pandemic will be identified by sites using clinical information about who is self monitoring their BP, these women will be approached by their usual care team or research midwives who will provide a PIS about the study and ask if they would be willing to be contacted by a qualitative researcher [remotely]. Authenticating the identity of the

participant will be in line with normal clinical care procedures. A verbal consent form will be used where the researcher will seek and record informed oral consent, after the women has had sufficient time to think about whether they want to take part. The interviews will be audio-recorded and transcribed. Transcripts will be coded in NVivo and analysed thematically.

## 10. Health economics sub-study

This aims to determine whether BP self-monitoring in addition to usual care represents value for money of NHS resources compared to usual care alone in a population of high risk pregnant women (BUMP 1) and women with a diagnosed of hypertension during pregnancy (BUMP 2). Two separate cost-effectiveness analyses with the methodology described below will be carried out alongside the trials.

Design: within-trial cost-utility analysis using individual patient-level data with a time horizon up to 2 months following delivery.

Health outcomes: the main health outcome measure in the economic evaluation will be quality-adjusted life years (QALYs) over the trial period. The calculation of a QALY profile for each woman will be informed using data from the health-related quality of life instrument EQ-5D-5L that will be collected at baseline, 30 weeks' gestation and final follow-up. A linear change between utility measures at each time period will be assumed when deriving individual's QALY profile.

Costs: Relevant healthcare resource use during pregnancy for mothers and their fetuses will be identified and included in the cost analysis. Antenatal and postnatal care up to hospital discharge will include community professionals and secondary care visits including hospital admissions. Intrapartum and related postnatal care before hospital discharge will include major procedures undertaken, length of stay, transfers and admissions to higher level of care by mothers and their babies. Primary and secondary care resource utilisation during the trial will be collected using case note review and electronic hospital records as appropriate including routine and additional clinic visits to midwives and GPs. The cost of using an automated monitor along with the telemonitoring system will be estimated and included in the cost analysis of the self-monitoring group in each trial.

## 11. SAFETY REPORTING

### 11.1. Definitions

| | |
|---|---|
| Adverse Event (AE) | Any untoward medical occurrence in a participant to who has receive the intervention, including occurrences which are not necessarily caused by or related to that intervention. |
| Serious Adverse Event (SAE) | A serious adverse event is any untoward medical occurrence that:<br>• results in death<br>• is life-threatening |

| | |
|---|---|
| | • requires inpatient hospitalisation or prolongation of existing hospitalisation<br>• results in persistent or significant disability/incapacity<br>• consists of a congenital anomaly or birth defect.<br><br>Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.<br><br>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. |

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

### 11.2. 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.

### 11.3. Procedures for Recording Adverse Events

We do not anticipate that the study intervention (self-monitoring of blood pressure) 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 who will inform the REC that gave favourable opinion. We will not report side effects as stated in the BNF as AEs.

### 11.4. 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 faxed and/or 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 Data Monitoring Committee (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 DMC for review. The DMC also monitors the frequency and pattern of events reported as part of its independent oversight of the trial.

### 11.5. Expectedness

We do not anticipate any serious adverse events due to the self-monitoring intervention or the qualitative studies.

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 in the acute situation and ratified by the steering group.

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.

# 12. STATISTICS

## 12.1. Description of Statistical Methods

All analyses will be carried out on an intention-to-treat basis. The association of missing outcomes with baseline factors will be investigated, and those factors found to be predictive of missingness will be included as additional fixed effects in the analyses.

External Pilot: Descriptive statistics will be used to describe the women included in the external pilot. A sensitivity analysis utilising the methods outline below will assess the effect of including the women in the external pilot with those randomised in the main trials.

**BUMP 1:** An intention to treat (ITT) analysis will include all those women recruited to BUMP 1. The primary analysis for BUMP 1, aims to determine if there is a difference in the time to diagnosis between the randomised groups, and will be performed using a two-stage linear hurdle model. The first equation models whether a person is diagnosed with hypertension or not and is modelled by means of a probit function. The second equation is a linear mixed effects model which models the time to diagnosis as a function of randomised group and parity, which are included as fixed effects. Site is accounted for by means of a random effect. In this way, all women who are recruited to BUMP 1 contribute to the primary analysis. Continuous secondary outcomes, such as birth weight and length of stay, will be analysed by means linear mixed effects models. Binary secondary outcomes, such as the development of severe hypertension, incidence of complications and incidence of stillbirth, will be analysed by means of a logistic mixed effects model, accounting for site as a random effect.

**BUMP 2:** An ITT analysis will include all those women recruited to BUMP 1 who become hypertensive and de novo to BUMP 2. The primary analysis for BUMP 2 will compare BPs between the intervention and control groups, and will include women recruited from BUMP 1 who become hypertensive and de novo to BUMP 2. Analysis of the BP outcome will be by means of a linear mixed effects model which can accommodate data where participants have unequal repeated measurements, and also accounts for missing data (assuming data are missing at random (MAR)). Each of a participant's BP measures will be modelled by means of a linear mixed effects model, including a random effect for recruitment site and participant and assuming an unstructured variance covariance matrix between measurements from the same participant. Time of BP measurement and randomised group, as well as their interaction term, will be included as fixed effects in the model. A fixed effect will also be included for whether the participant was from BUMP 1 or not. As a sensitivity analysis whether being included from BUMP1 or not will be tested as a moderator of the treatment effect. By means of appropriate contrasts, the difference in the mean BP of participants in the two randomised groups will be compared. BP load and area under the curve will be analysed as continuous outcomes by means of a linear mixed effects model, which includes recruitment site as a random effect and randomised group as a fixed effect. Whether the participant originated from BUMP 1 will be included as a fixed effect. Continuous secondary outcomes, such as birth weight and length of stay, will be analysed by means of linear mixed effects models. Binary secondary outcomes, such as the development of severe hypertension, incidence of complications and incidence of stillbirth, will be analysed by means of a logistic mixed effects model, accounting for site as a random effect.

### 12.2. The Number of Participants

**External Pilot:** An external pilot including up to 50 women from a single site will be undertaken to ensure that all trial procedures are operating as intended. No formal power calculation has been undertaken for this and it is envisaged that the majority of these women will be entered into BUMP2. As most trial procedures are shared between BUMP 1 and BUMP 2 this is felt to be appropriate.

**BUMP 1:** A sample size of 2262 (1131/group) assuming an standard deviation (SD) of 40 days would allow detection of an effect size of 12 days difference in time to detection of raised BP in pregnancy between self-monitoring and control groups (the primary outcome of BUMP 1), with 90% power and 5% level of significance (2-sided) and assuming a 15% attrition rate. If the SD is 45 days, this sample size will allow to detect a difference of 14 days with more than 90% power and if the SD is 50 days then it will be sufficient to detect a difference of 16 days in time to detection of raised BP in pregnancy also with 90% power. The sample size was determined via a simulation method which accounted for the skewed distribution of the outcome, determined from our pilot work in the BUMP study. Of the 2262 women recruited to BUMP 1, we would expect around 362 women to develop hypertension.

**BUMP 2:** BUMP 2 will assess the impact of self-monitoring of BP, in women with hypertension in pregnancy, on BP control. A sample size of 256 per group will be sufficient to detect a 5mmHg difference between groups, accounting for 15% attrition and an SD of 16mmHg, based on data from the BUMP pilot and PELICAN studies, inflated from 14mmHg because BUMP 2 will include hypertensive women from BUMP 1 and those with chronic or gestational hypertension not previously randomised in BUMP 1.

Women randomised in BUMP 1 will remain in their randomisation groups and move seamlessly into the BUMP 2 once they have been diagnosed with hypertension. Women developing gestational hypertension or who have chronic hypertension not in BUMP will be randomised to either usual care using clinic BP to guide treatment or self-monitoring with telemonitoring and automated feedback. The precise ratio of women migrating from BUMP1 and randomised de novo will not be fixed.

### 12.3. 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%.

### 12.4. Criteria for the Termination of the Trial

The trial is of a method of management rather than a medicinal product and is in addition to usual care. It is therefore considered low risk and no interim analysis is planned. Any consideration of the need for termination of the trial will be on the advice of the DMC and Trial Steering Committee (TSC) who will consider the need for prospective criteria for termination.

### 12.5. 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, 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. The need for a sensitivity analysis taking into account missing data using multiple imputation will be considered.

*Spurious data*: Spurious data will be assessed using standard editing criteria.

### 12.6. Inclusion in Analysis

All data will be included in the analysis as far as possible to allow full ITT analysis, though there will inevitably be the problem of missing data due to withdrawal, loss to follow-up, or non-response questionnaire items.

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

The final statistical 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.

### 12.8. Cost-effectiveness analysis

The main health outcome measure in the economic evaluation will be QALYs and the perspective of the analysis will be that of the UK NHS. Costs and outcomes will be synthesised using the incremental cost-effectiveness ratio which will be expressed as cost per QALY gained. Uncertainty around cost-effectiveness results will be primarily presented using cost-effectiveness acceptability curves and we will follow current guidance for methods of technology appraisal to present and report the results of the economic analysis.(15) If applicable, the results of the economic evaluation will also be presented using a cost-consequence analysis framework where the primary, selected secondary outcomes and costs from each trial will be presented in a disaggregated manner over the trial period.

## 13. DATA MANAGEMENT

### 13.1. 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), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, 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 locked cupboard in locked rooms with restricted access. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

### 13.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution (University of Oxford) and the regulatory authorities to permit trial-related monitoring, audits and inspections. 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.

### 13.3. 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 PC-CTU in line with the PC-CTU SOPs and will hold and allow data management of all data points required to conduct the final analysis. The clinical database will be built on an externally validated secure web-based platform allowing for data tracking by use of date stamped audit logs. A clinical data manager will be assigned to the study supervised by Oxford PC-CTU's Senior Clinical Data Specialist and PC-CTU SOPs will be followed.

## 14. QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current 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 TSC and DMEC will be convened. The precise terms of reference of the TSC and DMC, including frequency of meeting, will be agreed by the members.

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

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

## 15. SERIOUS BREACHES

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree –

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

(b) the scientific value of the trial".

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the

Sponsor will report it to the REC committee, Regulatory authority and the NHS host organisation within seven calendar days.

## 16. ETHICAL AND REGULATORY CONSIDERATIONS

### 16.1. Declaration of Helsinki

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

### 16.3. Approvals

The protocol, ICF, PIS and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), Health Research Authority (HRA), regulatory authorities, and host institution(s) for written approval.

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

### 16.4. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA , host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the REC, host organisation and Sponsor.

### 16.5. Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained in the trial database. The participants will be identified only by a participant ID number on all trial documents and any electronic database, with the exception of the CRF, where participant initials may be added. Women's identifiers (names, address, phone number) will be held securely and separately from the CRFs where they are needed to contact participants on an ongoing basis, eg for follow-up. Access to these data will be strictly on a need to know basis. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act and General Data Protection Regulation (GDPR) 2018, which requires data to be anonymised as soon as it is practical to do so.

### 16.6. Expenses and Benefits

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

## 17. FINANCE AND INSURANCE

### 17.1. Funding

The study is funded by the NIHR Programme Grants for Applied Health Research as part of a wider programme of work (RP-PG-0614-20005).

### 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.

## 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.

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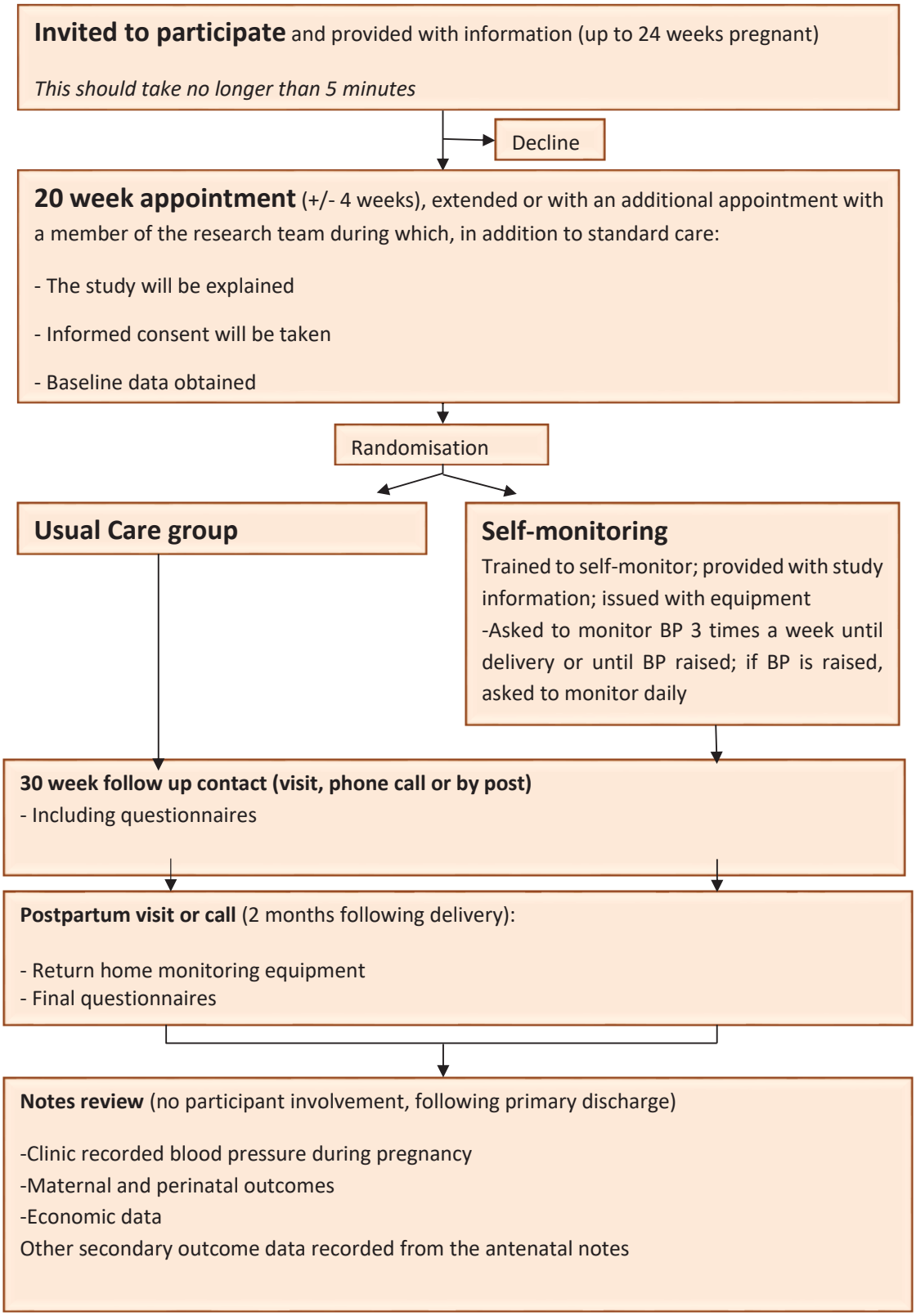
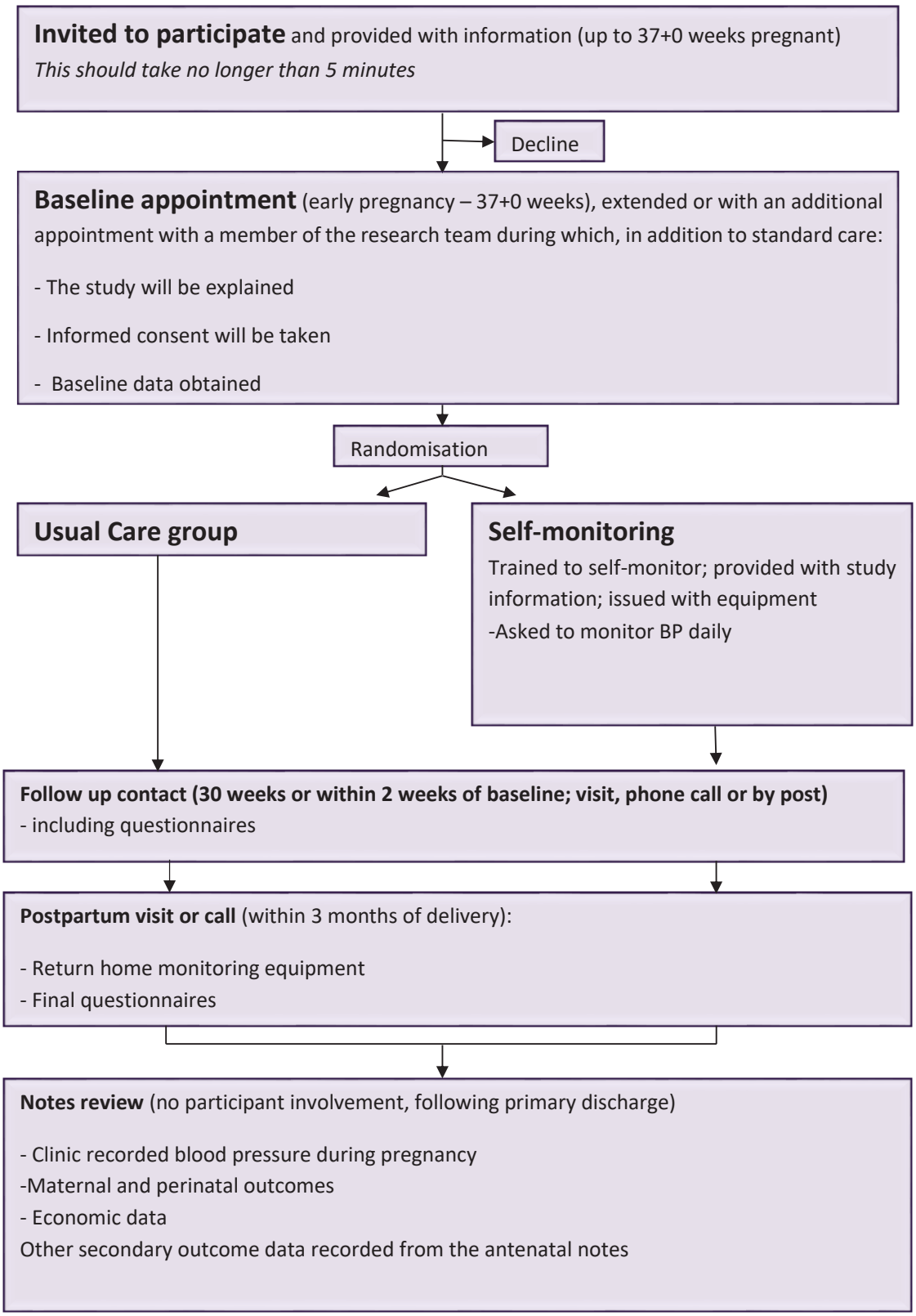
**APPENDIX 1: STUDY FLOW CHART BUMP 1**



**APPENDIX 2: STUDY FLOW CHART BUMP 2 for women not previously randomised in BUMP 1**

Note see Figure 1 study design for overview of flow from BUMP1 to BUMP2



## APPENDIX 3: INTERPRETATION CHART FOR BUMP 1

| LEVEL | BLOOD PRESSURE /mmHg | ACTION |
|---|---|---|
| **HIGH** | SYS 150 or more<br><br>OR<br><br>DIA 100 or more | Your blood pressure is high<br><br>Sit quietly for 5 minutes then measure it again and send in the reading.<br><br>Contact your maternity unit for urgent assessment today (within 4 hours) and continue to monitor your BP daily. |
| **RAISED** | SYS 140-149<br><br>OR<br><br>DIA 90-99 | Your blood pressure is raised<br><br>Sit quietly for 5 minutes then measure it again and send in the reading.<br><br>If your repeated reading is raised please contact your maternity unit within 24 hours and continue to monitor your BP daily. |
| **HIGH NORMAL** | SYS 135-139<br><br>OR<br><br>DIA 85-89 | Your blood pressure is normal but moving towards the raised threshold<br><br>Sit quietly for 5 minutes then measure it again and send in the reading.<br><br>If your repeat reading is still high-normal, please monitor your blood pressure daily. |
| **NORMAL** | SYS 110-134<br><br>OR<br><br>DIA 70-84 | Your blood pressure is normal.<br><br>Continue blood pressure monitoring and your current care |
| **LOW** | SYS 109 or less<br><br>AND<br><br>DIA 69 or less | Your blood pressure is low. Repeat once more in 5 minutes.<br><br>If you are taking blood pressure medication, contact your maternity unit within 24 hours or within 4 hours if you feel unwell (e.g. dizzy or faint).<br><br>If you are not taking medication and you are feeling well this blood pressure does not need any further action. |

## APPENDIX 4: INTERPRETATION CHART FOR BUMP 2

| LEVEL | BLOOD PRESSURE /mmHg | ACTION |
|---|---|---|
| **HIGH** | SYS 150 or more<br>OR<br>DIA 100 or more | Your blood pressure is high<br>Sit quietly for 5 minutes then measure it again and send in the reading.<br>Contact your maternity unit for urgent assessment today (within 4 hours) and continue to monitor your BP daily. |
| **RAISED** | SYS 140-149<br>OR<br>DIA 90-99 | Your blood pressure is raised<br>Sit quietly for 5 minutes then measure it again and send in the reading.<br>If your repeated reading is raised please contact your maternity unit within 24 hours and continue to monitor your BP daily. |
| **NORMAL** | SYS 110-139<br>OR<br>DIA 70-89 | Your blood pressure is normal.<br>Continue blood pressure monitoring and your current care |
| **LOW** | SYS 109 or less<br>AND<br>DIA 69 or less | Your blood pressure is low. Repeat once more in 5 minutes.<br>If you are taking blood pressure medication, contact your maternity unit within 24 hours or within 4 hours if you feel unwell (e.g. dizzy or faint).<br>If you are not taking medication and you are feeling well this blood pressure does not need any further action. |

**APPENDIX 4: AMENDMENT HISTORY**

| Amendment No. | Protocol Version No. | Date issued | Author(s) of changes | Details of Changes made |
|---|---|---|---|---|
| Minor Amendment 1 | 1.1 | 30.08.17 | Marloes Franssen (Trial manager) | Update in appendix 2 to match text in section 8 |
| Substantial Amendment 1 | 1.2 | 04.10.17 | Richard McManus (CI) | Add in paragraph indicating the trial will pilot up to 50 women at 1 site before the main trial |
| Substantial Amendment 2 | 2.0 | 12.10.18 | Greig Dougall (Trial manager) | Update to Qualitative sub-study information. Added details of two new qualitative studies (Section 9.0) Change of Trial Manager details. Minor change to section 16.5. GDPR update. |
| Substantial Amendment 4 | 2.1 | 12.06.19 | Greig Dougall (Trial manager) | Clarification to planned sample size to illustrate calculated sample size is the minimum number of participants to be recruited. |
| Substantial Amendment 5 | 3.0 | 24.10.2019 | Greig Dougall (Trial manager) | Update to Qualitative sub-study information. Added details of one new qualitative study (Section 9.0) and added information on participants receiving vouchers in QSS-2. |
| Minor Amendment 7 | 4.0 | 07.05.2020 | Greig Dougall (Trial Manager) | Update to qualitative sub-study 4 (QSS-4) information relating to an online survey option during the COVID-19 outbreak. |
| Substantial Amendment 6 | 5.0 | 03.06.20 | Katherine Tucker (lead research fellow - acting trial manager) | Update to qualitative work (Section 9) to recruit additional 30 women taking part in remote monitoring due to COVID-19 to be interviewed as part of substudy 4 (a new PIS and ICF are introduced for this purpose). |

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 or MHRA.