



## BUMP 2

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

SAP Version 1.0

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# 1 INTRODUCTION

## 1.1 PREFACE

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This SAP supports version 3.0 of the protocol dated 24<sup>TH</sup> Oct 2019. This SAP relates to the BUMP 2 section of the protocol only. A separate SAP has been prepared for the BUMP 1 section of the protocol.

## 1.2 PURPOSE AND SCOPE OF THE PLAN

This document details the proposed analysis of the main paper(s) reporting results from the NIHR programme grant for applied health research funded randomised controlled trial exploring whether self-monitoring of blood pressure to guide management of hypertension in pregnancy leads to better control of blood pressure compared to usual care. The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial. All example tables included in the plan are intended to aid the presentation of data at final analysis. However, the statistician should not be bound by these tables and is free to present the results in a suitable way.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

The details regarding analysis of the economic and qualitative sub studies will be presented in a separate analysis plan.

### 1.3 TRIAL OVERVIEW

Raised blood pressure (BP) affects approximately 10% of pregnancies worldwide, and a high proportion of affected women develop pre-eclampsia. Self-monitoring of BP in pregnancy could improve the management of hypertension in pregnancy, whilst also empowering and engaging women in their own care. This study aims to evaluate whether self-monitoring of BP in pregnancy in women with chronic or gestational hypertension leads to better control of blood pressure.

Once raised BP in pregnancy is detected (or pre-existing), the clinical focus is to treat the BP, monitor for development of pre-eclampsia and to ensure appropriate foetal surveillance. 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 allows for multiple measurements with little or no disturbance of lifestyle and is now common place in adults with hypertension. Self-monitoring has advantages in terms of estimating the underlying BP better than intermittent clinic measurements and, in the context of pregnancy, enabling the management of raised BP when it happens as opposed to waiting for periodic appointments with a healthcare professional.

### 1.4 OBJECTIVES

The primary objective is to evaluate whether self-monitoring of BP reduces systolic BP in women with hypertension in pregnancy.

The secondary objectives are as follows:

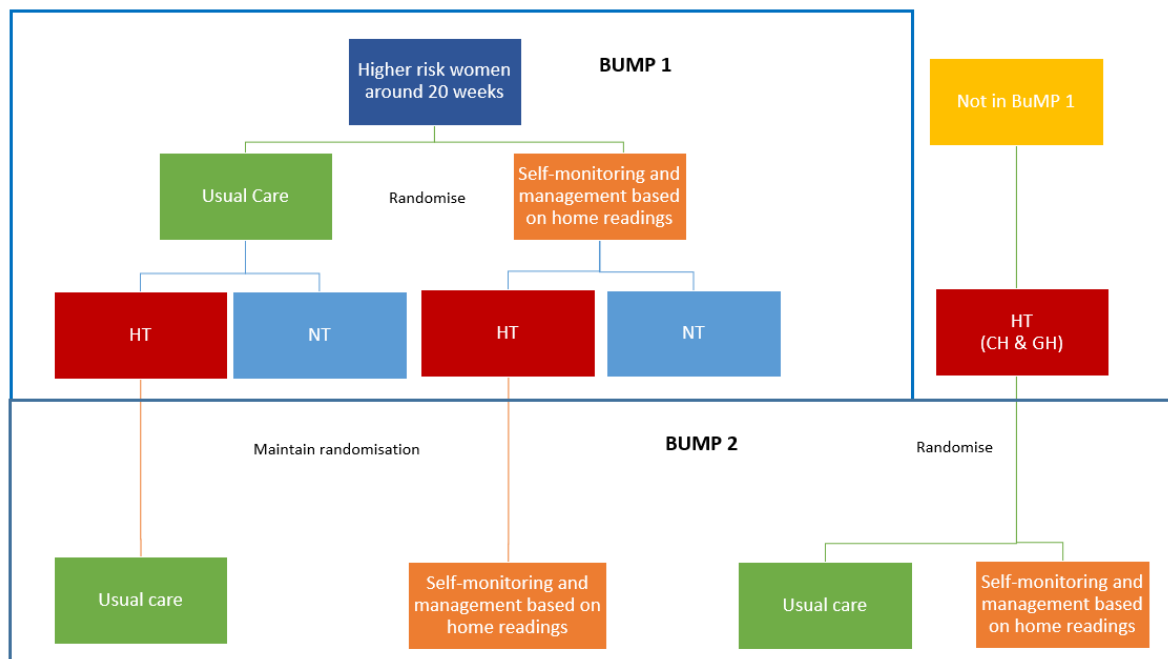
1. To evaluate the effect of self-monitoring of BP on other measures of BP in hypertension in pregnancy.
2. To evaluate the effect of self-monitoring of BP in hypertension in pregnancy on maternal and perinatal adverse outcomes.
3. To evaluate whether self-monitoring of BP in hypertension in pregnancy affects quality of life and is cost effective.
4. To evaluate how self-monitoring of BP in hypertension in pregnancy is implemented in daily life and routine clinical practice.

## 2 TRIAL DESIGN

BUMP 2 is a prospective non-masked randomised controlled trial. Participants are randomised to either usual care or self-monitoring and management based on home readings with an allocation ratio of 1:1. The trial population are women with chronic hypertension or gestational hypertension. Women may enter this study from BUMP 1 (maintaining their original randomisation) or be recruited with chronic or gestational hypertension without prior involvement in BUMP 1 (*de novo*).

Planned study procedures and timings are shown in Appendix I.

The figure below explains the potential flow of participants from BUMP 1 to BUMP 2.



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

## 2.1 OUTCOMES MEASURES

Definitions and Derivations of primary and secondary outcomes are detailed in section 3.

### 2.1.1 PRIMARY OUTCOME

The primary outcome is the mean of all systolic BP readings recorded by health care professionals, from post-entry into the study until up to one day before the date of delivery.

### 2.1.2 SECONDARY OUTCOMES

With the exception of EQ-5D-5L, STAI-6, MARS-5, (Adapted) Brief-IPQ and Adapted beliefs about medicines questionnaire, all secondary outcomes will be established from a notes review, which will take place following primary discharge. EQ-5D-5L, STAI-6 and Adapted beliefs about medicines questionnaire will be measured at baseline, follow up (around 30 weeks or 2 weeks after starting the intervention if randomised after 30 weeks) and 8 weeks postpartum. The MARS-5 questionnaire will be measured at 30-week follow-up and 8 weeks postpartum

The following are maternal outcomes and relate to secondary objectives 1 and 2.

- Mean clinic measured diastolic BP from post-entry to the study (as above for systolic blood pressure) up to one day before the day of delivery
- Time-weighted average systolic and diastolic *clinic* blood pressures (using an area under the curve analysis with the trapezium rule)
- Number and proportion of women with systolic BP $\geq$ 140mmHg and/or diastolic BP $\geq$ 90 mmHg, as measured by a health care professional
- Number and proportion of women with severe hypertension (systolic BP $\geq$ 160mmHg and/or diastolic BP $\geq$ 110mmHg) as measured by a health care professional
- Number and proportion of women with pre-eclampsia
- Number and proportion of women with each of the following serious maternal complications
  - Transient ischemic attack or stroke
  - Pulmonary oedema
  - Renal failure (aka renal involvement)
  - Eclampsia
  - HELLP syndrome (haemolysis, elevated liver enzymes, low platelets)
  - Liver involvement (ALT or AST >70 U/L)
  - Haematological involvement (platelets < $\times 100^9$ /L)
- Number and proportion of women experiencing one or more of the serious maternal complications listed above
- Number and proportion of women requiring a blood transfusion
- Number and proportion of women who died
- Onset of labour
  - Type: spontaneous, induction, pre-labour caesarean section, pre-labour rupture of membranes/stimulation of labour
  - Indication: if woman recorded as having an induction of labour or a pre labour caesarean section (pre-eclampsia, chronic hypertension only (or gestational hypertension only), other medical complication, reaching 37 weeks gestation, maternal hypertension not controlled by maximal therapy, maternal haematological abnormality, maternal biochemical abnormality, fetal concern on ultrasound scan, fetal compromise on cardiotocography, severe maternal

symptoms, preterm pre labour rupture of membranes, antepartum haemorrhage, fetal growth restriction, twins, other)

- Quality of Life (EQ-5D-5L) (Index value and VAS)

The following are perinatal outcomes and relate to secondary objective 2.:

- Number and proportion of stillbirths
- Number and proportion of early neonatal deaths, occurring during the first seven days of life (0-6 days),
- Gestation at delivery (weeks: decimal to denote days e.g. 34+2 would be 34.29 weeks)
- Mode of delivery
- Birthweight
- Centile of birthweight
- Number and proportion of infants <10<sup>th</sup> centile for birthweight
- Number and proportion of infants <3<sup>rd</sup> centile for birthweight
- Number and proportion of infants admitted to the neonatal unit
- Length of stay in the neonatal unit

The following are process outcomes and relate to secondary objectives 3 and 4.

- Fidelity to monitoring schedule (% of expected readings and proportion with at least 90% of expected readings)
- Adapted beliefs about medicines questionnaire
- Adherence to medication: MARS questionnaire
- State-Trait Anxiety Inventory (STAI-6) short form anxiety questionnaire
- Self-efficacy questionnaire assessing health behaviours

## 2.2 TARGET POPULATION

Two separate groups of women will be eligible: i) women in BUMP 1 that develop raised BP prior to birth and ii) pregnant women with chronic or gestational hypertension recruited de novo and not in BUMP 1. For the analysis there will be two distinct groups of women, 1) those (almost exclusively recruited de novo in BUMP2) with chronic hypertension and 2) those with gestation hypertension who will have been recruited both de novo in BUMP2 (approx. 25%) and those recruited originally in BUMP1 who develop raised BP prior to birth. Primary analyses described below will be by these two subgroups of gestational and chronic hypertension.

### **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 $\geq$ 140 mmHg and/or diastolic BP $\geq$ 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 $\geq$ 140 mmHg and/or diastolic BP $\geq$ 90 mmHg).



- Recruited at between 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.

#### **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)

### **2.3 SAMPLE SIZE**

The original power calculation for BUMP2 estimated that a sample size of 256 per group would be sufficient to detect a 5mmHg difference between groups, accounting for 15% attrition and a 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. The calculation assumed 90% power and a 5% level of significance (2-sided).

The planned sample size was 512 recruited *de novo* plus any graduating from BUMP 1. This was subsequently inflated to 600 (substantial amendment 4) *de novo* plus graduates in view of the concern to recruit sufficient numbers to retain power in both gestational and chronic hypertensives as far as possible.

### **2.4 RANDOMISATION AND BLINDING IN THE ANALYSIS STAGE**

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 recruited *de novo* will be randomly 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 (0 or  $\geq 1$ ). 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.

### 3 DEFINITIONS AND DERIVATION OF VARIABLES

#### 3.1 DEFINITIONS

##### 3.1.1 DATE OF ENTRY INTO STUDY

This is the date of randomisation for the women recruited into the study *de novo*.

For women who transfer into BUMP2 from BUMP1, this will be the date on which they fulfil the criteria for the diagnosis of hypertension in BUMP 1 (i.e. Sustained systolic BP  $\geq 140$  and/or diastolic BP  $\geq 90$  mm Hg OR The woman has received a new prescription of antihypertensive medication for raised blood pressure). The date of entry into BUMP2 will be the date of primary outcome as derived from BUMP 1 analysis.

##### 3.1.2 HEALTHCARE PROFESSIONAL-MEASURED BP MEASUREMENT

This is any BP measurement taken by a health care professional (i.e. any BP measurement taken at standard antenatal appointment, MAU/DAU and during hospital (ward) admission prior to delivery).

##### 3.1.3 BASELINE BP MEASUREMENT

For women recruited *de novo*, (a) this is the baseline BP measurement recorded on the CRF.

For women transferring from BUMP 1 (b), this will be depend on whether the date of entry is defined by (i) the date of the second high BP reading or (ii) receiving a new prescription of antihypertensive medication.

For:

(a) baseline BP measurement will be the healthcare professional-measured reading taken on the date of entry. If there is no BP recorded on date of entry then the healthcare professional-measured reading(s) immediately prior to study entry will be used

(b) it will be the last healthcare professional-measured BP reading(s) before the date of entry for those with two high BP readings and healthcare professional-measured reading on date of entry for those with a new prescription. If unavailable for the latter, the last healthcare professional-measured reading(s) prior to transitioning will be used.

If there is more than one clinic/DAU/MAU reading on the day of baseline BP measurement, then the average of the three readings will be used. For measurements taken on the ward, the highest BP reading will be used.

##### 3.1.4 'POST-ENTRY' READINGS

For the *de novo* group, this will be all BP readings taken after date of randomisation into the study (i.e. date of entry + 1).

For women transferring into BUMP 2, this will be all readings taken after date of entry into the BUMP 2 study (i.e. date of entry +1).

The date of entry into BUMP2 from BUMP 1, as well as all healthcare professional-measured blood pressure measurements will be established by means of a notes review, carried out following primary discharge. Syntax for the derivation of the primary outcome in BUMP1 (i.e. date of entry to BUMP2) will be shared from BUMP1.

## 3.2 DERIVATIONS

### 3.2.1 INDICATION OF TRANSFER FROM BUMP 1

This will need to be determined from the variable *b1b2*, where *b1b2=1* indicates recruitment into BUMP1 and determining which of these women reach the primary outcome for BUMP1..

### 3.2.2 CLASSIFYING HYPERTENSION COHORTS

As the analyses will be done separately for the gestational and chronic hypertension cohorts, a variable will be created identifying which cohort each women belongs to. This can be done as follows:

#### 3.2.2.1 GESTATIONAL HYPERTENSION COHORT

For the *de novo* recruits, gestational hypertension can be determined from the variable *ic5\_bl2 =1* (*ic5\_bl2* indicates whether or not a woman develops hypertension after 20 weeks' gestation).

For those transferring from BUMP 1, women who were newly diagnosed cases of gestational hypertension in BUMP 1 can be identified from the variable *diagnote1\_nr=2*. All women transferring from BUMP 1 should be gestational hypertension cases.

#### 3.2.2.2 CHRONIC HYPERTENSION COHORT

For the *de novo* recruits, cases with chronic hypertension can be determined from the variable *ic4\_bl2 =1*.

For those transferring from BUMP 1, newly diagnosed cases of chronic hypertension are not expected.

### 3.2.3 SITE

It will be derived from the middle 3 digits of the participant ID [*record\_id*] (Refer to Appendix III for a list of the current sites and their codes).

### 3.2.4 DELIVERY BEFORE PRIMARY OUTCOME RECORDED/ DELIVERY WITHIN 2 DAYS OF RECRUITMENT (Y/N)

For women that are recruited late into pregnancy, if a delivery occurs before any BPs are measured, a variable will be derived, using the date of entry into the study, indicating 'delivery before primary outcome recorded'/ 'delivery within 2 days of recruitment'.

### 3.2.5 TWIN PREGNANCY (Y/N)

An indication of a twin pregnancy is found in the variable *mhtwin\_bl2=1*

### 3.2.6 PRIMARY OUTCOME

Each participant will have recorded in the eCRF, up to three BP measurements taken at each clinic, Day Assessment Unit (DAU)/Maternity Assessment Unit (MAU) visit since randomisation and also the highest BP taken on each day of admission to the ward up to date of delivery minus 1 day.

The primary outcome is the average mean daily systolic BP recorded by health care professionals, over all measurements taken from date of entry to BUMP2 plus 1 day, until the date of delivery minus 1 day. This outcome will be derived for each woman from variables recorded in the case report forms (CRF) by averaging the daily measurements then taking the mean of these to obtain one measurement per woman over their time in the study. As there are unlikely to be three clinic/DAU/MAU measurements per visit, all available measurements per visit per day will be used in the calculations. If there are more than three clinic readings on any day, then the first three readings will be used. For measurements taken on the ward, the highest BP reading is recorded and will be used.

#### Variables required

The following questions (15a, 15b, 16 and 17) from the notes review CRF are required to determine the mean systolic blood pressure for each participant over their time in the study. For the women recruited *de novo*, question 15a should contain the blood pressure readings pre-randomisation, while for the women transferring from BUMP 1, the pre-entry blood pressure measurements are the baseline measurements defined in section 3.1.3. For all participants, the clinic blood pressure readings post-study entry should be in question 15b, DAU/MAU BP readings in question 16 and the highest blood pressure readings on each day of a ward admission in question 17.

***Due to data entry errors, the date (as opposed to question number) will be used to generate an indicator variable to classify whether the BP readings are pre- or post-study entry:***

The variable names for the date and blood pressure readings, by source and time-point, are: last clinic visit prior to entry into the study [pcbpdat\_nr, pcbpfsys\_nr, pcbpssys\_nr and pcbptsys\_nr]; post study entry [cbpdat01\_nr, cbpfsys01\_nr, cbpssys01\_nr, cbptsys01\_nr etc. with incremental numbering]

### 3.2.7 SECONDARY OUTCOMES - BINARY

#### 3.2.7.1 PROPORTION OF HEALTHCARE PROFESSIONAL-MEASURED SYSTOLIC BLOOD PRESSURE READINGS $\geq 140$ MMHG

For each woman, the percentage of days with a reading meeting the criteria will be calculated as ((Number days with any SBP readings  $\geq 140$ mmHg / total number of days with BP readings) x 100)

In addition, summary statistics (no statistical comparison) by treatment group will be presented for the number and proportions with:

- 1) DBP  $\geq 90$  mmHg, and
- 2) SBP  $\geq 140$  mmHg AND/OR DBP  $\geq 90$  mmHg

### 3.2.7.2 PROPORTION OF WOMEN WITH SEVERE HYPERTENSION

Sustained severe hypertension is defined as systolic BP $\geq$ 160mmHg and/or diastolic BP $\geq$ 110mmHg from any health care professional-measured BP recorded (post entry into BUMP 2) in the notes review. For sustained, at least two high readings within 1 week (7 days / 168 hours) need to be recorded (with no minimum time between readings). This can include 2 high SBP readings, 2 high DBP readings, or one high SBP and one high DBP reading.

The average BP measurements per visit will be derived as follows:

For each day BP has been recorded, the average SBP and DBP will be computed as the mean of all measurements. A binary variable (Yes/No) will be derived to indicate if the average SBP is  $\geq$ 160mmHg, and another binary variable will be derived to indicate if average DBP  $\geq$ 110mmHg. These will then be combined into an outcome variable indicating severe hypertension when either BP type or a combination of them is high within 1 week. For each woman, a variable will be created indicating if they had sustained severe hypertension within any 7 day period. The proportion with sustained severe hypertension will be calculated as:

[Number of women with sustained severe hypertension / number of women for whom primary outcome data are available] x 100

### 3.2.7.3 PROPORTION OF WOMEN WITH PRE-ECLAMPSIA

The proportion of women with pre-eclampsia will be calculated from question 7 of the notes review CRF. A woman has pre-eclampsia if *diagnote2\_nr*=2. If the notes review has been carried out and the response to this question is missing, it will be assumed that the woman was not diagnosed with pre-eclampsia.

The denominator is the number of women for whom primary outcome data are available.

### 3.2.7.4 PROPORTION OF WOMEN WITH SERIOUS MATERNAL COMPLICATIONS

The proportion of women with each of the following serious maternal complications will be calculated from questions 7b of the notes review CRF. If the notes review has been carried out and the response to a question is missing, it will be assumed that the woman did not experience that event. In each case, the denominator is the number of women for whom primary outcome data are available.

- Eclampsia [*pdeclam\_nr*=1]
- Transient ischemic attack or stroke [*pdtias\_nr*=1]
- HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) [*pdhellp\_nr*=1]
- Liver involvement (ALT or AST >70 U/L) [*pdliver\_nr*=1]
- Pulmonary oedema [*pdpo\_nr*=1]
- Renal involvement (creatinine $\geq$ 90mmol) [*pdrenal\_nr*=1]
- Haematological involvement (platelets  $<$ x100<sup>9</sup>/L) [*prhaem\_nr*=1]

### 3.2.7.5 PROPORTION OF WOMEN EXPERIENCING ONE OR MORE SERIOUS MATERNAL COMPLICATION

The proportion of women experiencing one or more serious maternal complication listed in section 3.8.4 will be calculated. The woman will be classified as having at least one serious maternal complication if any of the above variables are 1. If the notes review has been carried out and the response to a question is missing, it will be assumed that the woman did not experience that event. The denominator is the number of women for whom primary outcome data are available.

### 3.2.7.6 PROPORTION OF WOMEN REQUIRING A BLOOD TRANSFUSION

A woman will be classified as having had a blood transfusion if the answer to question 9 on the notes review CRF is yes (*transfu\_nr*=1). If the notes review has been carried out and the response to this question is missing, it will be assumed that the woman did not require a blood transfusion. The denominator is the number of women for whom primary outcome data are available.

### 3.2.7.7 PROPORTION OF WOMEN WHO DIED

Information on maternal deaths is recorded in question 10 of the notes review. A woman is recorded as having died if the variable *outcome\_nr*=3. The number (%) of deaths will be summarised by treatment arm. If the notes review has been carried out but none of the responses (discharged home (=1), transferred to another hospital (=2), died prior to discharge (=3)) have been recorded it will be assumed that the woman has been discharged home. The denominator is the number of women for whom primary outcome data are available.

### 3.2.7.8 PROPORTION OF WOMEN WITH SPONTANEOUS ONSET OF LABOUR

A woman will be classed as having a spontaneous onset of labour if the variable *onslab\_nr* = 1. All other categories of this variable [*onslab\_nr* = 2, 3 or 4] will be combined and classed as 'not having a spontaneous onset of labour'. If the notes review is completed and no responses are recorded, then assume spontaneous labour has occurred. .

The denominator here is the number of women who deliver at least one baby from 24/40 weeks onwards.

### 3.2.7.9 PROPORTION OF STILLBIRTHS

Information about stillbirths is recorded in question 2 of the notes review. A baby is recorded as having been stillborn if the variable *stabeop\_nr*=2. If none of the responses (live birth (=1), still birth (=2), miscarriage<24 weeks (=3), termination of pregnancy (=4)) have been recorded, this outcome will be assumed to be missing.

The variable *stabeop2\_nr* will be required for twin pregnancies.

i.e. Number of still births / total number of fetuses born from 24/40 weeks (ie counting twins as two individuals provided that they survive past 24/40 weeks; if one twin dies before 24/40 weeks then only one fetus is counted in the denominator)

### 3.2.7.10 PROPORTION OF EARLY NEONATAL DEATHS

An early neonatal death is defined as one occurring within 7 days of delivery. Question 14 of the notes review [*outcob1\_nr*] indicates the baby's outcome. If the baby died prior to discharge [*outcob1\_nr*=3] AND the difference between the date of delivery [*dodlvry\_nr*] and date of death [*discb1\_nr*] is <7 days, this will be classified as an early neonatal death. If the notes review has been carried out but none of the responses to question 14 (discharged home (=1), transferred to another hospital (=2), died prior to discharge (=3)) have been recorded, it will be assumed that the baby has been discharged home.

The variables *outcob2\_nr* and *discb2\_nr* will be required for twin pregnancies.

The proportion of early neonatal deaths per group will be computed as:  
number of early neonatal deaths / total number of births (alive or dead) from 24/40 weeks where each baby is counted once.

### 3.2.7.11 PROPORTION OF BABIES SMALL FOR GESTATIONAL AGE (<10<sup>TH</sup> AND <3<sup>RD</sup> CENTILE)

The birthweight centile for each baby will be calculated from population norms based on birthweight [weight1\_nr], sex [sex1\_nr] and gestation at delivery [weeks: gesteopw\_nr, days: gesteopd\_nr]. The intergrowth-21<sup>st</sup> application [newborn size] will be used to calculate the centiles (<https://intergrowth21.tghn.org/intergrowth-21st-applications/>). In order to use the application, gestation needs to be in days and birthweight needs to be in kilograms (with up to 3 decimal places). The proportion of babies with centile <10 and the proportion with centile <3 will be calculated.

If one or more of birthweight, sex or gestation at delivery are missing, then the birthweight centile will be missing. If the sex of the baby is recorded as 'ambiguous' [sex1\_nr=2 or sex2\_nr=2], an attempt will be made to find out what sex the baby has since been assigned. If this is not possible then the birthweight centile will be missing.

The variables *weight2\_nr* and *sex2\_nr* will be required for twin pregnancies. The denominator is all births (alive or dead) from 24/40 weeks.

### 3.2.7.12 PROPORTION OF INFANTS ADMITTED TO THE NEONATAL UNIT

Information about admissions to the neonatal unit is recorded in question 13 of the notes review. A baby is recorded as having been admitted to the neonatal unit if the variable *neonat1\_nr*=1. If the notes review has been carried out and the response to this question is missing, it will be assumed that the baby was not admitted to the neonatal unit.

The variable *neonat2\_nr* will also be required for twin pregnancies. The denominator is all births (alive or dead) from 24/40 weeks.

### 3.2.7.13 PROPORTION OF BABIES DELIVERED BY SPONTANEOUS VAGINAL DELIVERY

A baby will be classed as being delivered by spontaneous vaginal delivery if the variable *mode\_nr* = 1. All other options will be classed as not having a spontaneous vaginal delivery [*mode\_nr* = 2, 3, 4 or 5].

The variable *mode2\_nr* will also be required for twin pregnancies. The denominator is all births (alive or dead) from 24/40.

### 3.2.7.14 FIDELITY TO MONITORING SCHEDULE- PROPORTION OF DAYS WITH AN EXPECTED HOME BLOOD PRESSURE READING

**Note: This outcome is only applicable to the intervention group and the data will be obtained from the tele-monitoring dataset.**

Participants in this study are expected to have 7 home BP readings per week. Measurement taken between entering the study and the first of either pregnancy loss or delivery will be considered.

Descriptive statistics are to be presented separately for the GH and CH cohorts. Thereafter, within the GH cohort, descriptive statistics are to be presented separately for those who started in BUMP 1 and the *de novo* recruits.

The percentage of days with readings will be calculated as:  
(Number of days with readings carried out/Number of days with expected readings) x 100.

### 3.2.8 SECONDARY OUTCOMES – CONTINUOUS

#### 3.2.8.1 MEAN CLINIC MEASURED DIASTOLIC BLOOD PRESSURE

The mean diastolic blood pressure as recorded by health care professionals, from Date of entry) to the day before delivery will be calculated in exactly the same way as done for SBP for the primary outcome.

#### 3.2.8.2 AREA UNDER THE CURVE OVER TIME FOR BLOOD PRESSURE

AUC will be calculated using the trapezoid rule (<https://www.intmath.com/integration/5-trapezoidal-rule.php>) and will adjust for gestational time. The analysis will be carried out separately on the AUC for mean SBP and mean DBP measurements calculated for the primary and secondary outcomes above. One value per participant (e.g. gestational time-weighted mean clinic systolic or diastolic blood pressure between study entry and delivery) will be analysed.

#### 3.2.8.3 EQ5D VAS AND INDEX VALUE

The EQ-5D-5L (a five domain, five level) quality of life questionnaire is administered at baseline, 30 week follow up and postnatal follow up. Summary statistics for both the VAS and Index value will be presented for both treatment arms at all 3 time points.

- The EQ5D VAS [eq5d6] is measured on a scale from 0-100 where 100 = best health you can imagine and 0 = worst health you can imagine.
- The Index value is a single measure based on the five Eq-5D dimensions (Mobility [eq5d1], Self-care [eq5d2], Usual activities [eq5d3], Pain/Discomfort [eq5d4] and Anxiety/Depression [eq5d5]). It will be calculated using the Crosswalk calculation tool.

#### 3.2.8.4 GESTATION AT DELIVERY

Question 1 of the notes review collects gestation at delivery. It is recorded as 2 separate variables: [gesteopw\_nr] records the weeks and [gesteopd\_nr] records the days. Gestation at delivery will be converted from weeks and days to weeks by adding the days/7 to the weeks. For twins, gestation at delivery will be calculated for each child separately as these may differ.

#### 3.2.8.5 BIRTH WEIGHT

Birthweight of the baby is recorded in question 11 of the notes review and is measured in grams. The variable to be used is *weight1\_nr*.

The variable *weight2\_nr* will be required for twin pregnancies.

Mean birth weight needs to include all births (alive or dead) from 24/40 weeks; counting twins as two babies.

#### 3.2.8.6 BIRTH WEIGHT CENTILE

The birthweight centile for each baby will be calculated as described in section 3.2.7.11.



### 3.2.8.7 LENGTH OF STAY ON NEONATAL UNIT

**Note: Length of stay will be summarised/analysed only for those babies admitted to the neonatal unit.**

Information on admissions to the neonatal unit is recorded in question 13 of the notes review. A baby is recorded as having been admitted to the neonatal unit if the variable *neonat1\_nr=1*. If they had an admission to the neonatal unit then the number of nights spent on the unit is recorded in the variable *night1\_nr*.

The variables *neonat2\_nr* and *night2\_nr* will also be required for twin pregnancies.

### 3.2.8.8 FIDELITY TO MONITORING SCHEDULE (MEAN PERCENTAGE)

**Note: This outcome is only applicable to the intervention group and the data will be obtained from the tele-monitoring dataset.**

Descriptive statistics are to be presented separately for the GH and CH cohorts. Thereafter, within the GH cohort, descriptive statistics are to be presented separately for those who started in BUMP 1 and the *de novo* recruits.

The mean percentage of expected readings will be presented here, where the percentages will be calculated in section 3.2.7.14.

### 3.2.8.9 MEDICATION ADHERENCE REPORT SCALE (MARS-5)

Medication adherence is measured at 30 weeks and at postnatal follow up using the self-reported Medication Adherence Report Scale questionnaire. This MARS-5 questionnaire is only completed if participants respond 'yes' to the *bpmedp* variables at each time point. There are 5 self-reported questions, each with a range of responses from 1 (Always)-5 (Never). The score is summarised as the total of the 5 responses, giving a possible range of 5-25. A higher score indicates better self-reported adherence. MARS is likely to produce highly skewed scores so medians, IQR and ranges will be presented, along with divergent stacked bar graphs showing the frequencies of the responses for each of the five items.

MARS question	Variable names		
	Baseline	30 week follow-up	Postnatal follow-up
M1- I forget to take my medicines	mars1_bl2	mars1_fu	mars1_pfu
M2- I alter the dose of my medicines	mars2_bl2	mars2_fu	mars2_pfu
M3- I stop taking my medicines for a while	mars3_bl2	mars3_fu	mars3_pfu
M4- I decide to miss out a dose	mars4_bl2	mars4_fu	mars4_pfu
M5- I take less than instructed	mars5_bl2	mars5_fu	mars5_pfu

### 3.2.8.10 STAI-6 SHORT FORM ANXIETY QUESTIONNAIRE

Anxiety is measured using the short form of the State Trait Anxiety Inventory (**STAI**) at 30 weeks and postnatal follow up. The short form STAI includes 6 statements with responses from ‘not at all’ to ‘very much’.

Responses are scored as ‘not at all’ = 1 to ‘very much’ =4. Reverse scoring is required for the positive items (calm, relaxed, content) such that 1=4, 2=3, 3=2 and 4=1. The total score ranges from 6 to 24. These are scaled to be out of 100 by multiplying each individual’s total score by 20/6 to allow comparison to the full version of STAI for which population norms are published.

STAI question	Variable names		
	Baseline	30 week follow-up	Postnatal follow-up
I feel calm	calm_bl2	calm_fu	calm_pfu
I am tense	tense_bl2	tense_fu	tense_pfu
I feel upset	upset_bl2	upset_fu	upset_pfu
I feel relaxed	relax_bl2	relax_fu	relax_pfu
I feel content	cont_bl2	cont_fu	cont_pfu
I am worried	worri_bl2	worri_fu	worri_pfu

## 3.2.9 SECONDARY OUTCOMES – CATEGORICAL

### 3.2.9.1 MODE OF DELIVERY

Mode of delivery is recorded in the variable *mode\_nr* and consists of 5 categories. The denominator is all births (alive or dead) from 24/40 weeks.

The variable *mode2\_nr* will also be required for twin pregnancies.

## 4 ANALYSIS – GENERAL CONSIDERATIONS

### 4.1 DESCRIPTIVE STATISTICS

Continuous variables will be presented as means with standard deviations (SD), medians with interquartile ranges (IQR), as well as ranges (min; max), by treatment group. Binary and categorical variables will be reported as counts and percentages in each treatment group. Difference in means, with 95% confidence intervals, will be presented for all continuous outcome variables. Where appropriate, the difference in medians with 95% confidence interval will be used.

For binary outcome variables the proportion within each group, alongside the odds ratio and 95% confidence interval will be presented.

All the analyses specified in sections 5 and 6 will be carried out separately for the gestational hypertension cohort and chronic hypertension cohorts due to the varying gestations at recruitment, and therefore length of intervention, for women in the two cohorts

### 4.2 CHARACTERISTICS OF PARTICIPANTS

Summary statistics of baseline demographic and clinical variables by treatment group will be assessed to ensure balance of these characteristics between the two randomised groups. Number with missing data for each characteristic will also be presented. No formal statistical testing will be applied to test for any difference between randomised groups with respect to the baseline characteristics and no confidence intervals will be presented.

Patient flow from screening through randomisation, follow up and analysis will be presented in a CONSORT flow chart (Appendix II).

***Note for the CONSORT: Pregnancy loss is not a discontinuation but an outcome. It was used purely as a marker on REDCap to note that the participant should not have any further follow-up because of a pregnancy loss.***

TABLE 1: BASELINE CHARACTERISTICS BY RANDOMISED GROUP (GESTATIONAL HYPERTENSION COHORT)

	USUAL CARE N=	SELF MONITORING N=	OVERALL N N=
<b>Age (years)</b> [age_bl2]	Mean (SD) Median (IQR) (Range)	Mean (SD) Median (IQR) (Range)	Mean (SD) Median (IQR) (Range)
<b>Gestation (weeks) at entry into BUMP 2</b> [gestw_bl2]	Mean (SD) Median (IQR) (Range)	Mean (SD) Median (IQR) (Range)	Mean (SD) Median (IQR) (Range)
<b>Parity*</b> [pari1_bl2]	N(%)	N(%)	N(%)
0			
1			
2			
3			
4			
5			
>5			

<b>BMI (kg/m<sup>2</sup>)</b> [ <i>bmi_bl2</i> ]	Mean (SD) Median (IQR) (Range)	Mean (SD) Median (IQR) (Range)	Mean (SD) Median (IQR) (Range)
<b>Pregnancy interval &gt;10 years</b> [ <i>mhg10y_bl2</i> ]	N(%)	N(%)	N(%)
<b>Family history of pre-eclampsia</b> [ <i>mhclam_bl2</i> ]	N(%)	N(%)	N(%)
<b>Previous history of gestation hypertension or pre-eclampsia</b> [ <i>mhgest_bl2</i> ]	N(%)	N(%)	N(%)
<b>Chronic kidney disease</b> <i>mhckd_bl2</i>	N(%)	N(%)	N(%)
<b>Twin pregnancy</b> [ <i>mhtwin_bl2</i> ]	N(%)	N(%)	N(%)
<b>Diabetes</b> [ <i>mhdia_bl2</i> ]	N(%)	N(%)	N(%)
<b>Autoimmune disease</b> [ <i>mhaid_bl2</i> ]	N(%)	N(%)	N(%)
<b>Current smoker</b> [ <i>smoke_bl2</i> ]	N(%)	N(%)	N(%)
<b>Have you measured your blood pressure in this pregnancy?</b> [ <i>Bpmeas_bl2</i> ]	N(%)	N(%)	N(%)
<b>Ethnic group:</b> [ <i>ethnic_bl2</i> ] Asian or Asian British Black or Black British Chinese Mixed White British White Irish Other	N(%)	N(%)	N(%)
<b>Highest qualification:</b> [ <i>edlevel_bl2</i> ] Post graduate or above First degree Professional Qualifications A-level or equivalent GCSE, O-Level or CSE Vocational qualifications No formal qualifications	N(%)	N(%)	N(%)
<b>Mean baseline blood pressure (as defined previously)^:</b> Systolic BP  Diastolic BP	Mean (SD) Median (IQR) (Range) Mean (SD) Median (IQR) (Range)	Mean (SD) Median (IQR) (Range) Mean (SD) Median (IQR) (Range)	Mean (SD) Median (IQR) (Range) Mean (SD) Median (IQR) (Range)
<b>EQ5D VAS</b>	Mean (SD) Median (IQR) (Range)	Mean (SD) Median (IQR) (Range)	Mean (SD) Median (IQR) (Range)
<b>EQ5D Index Value</b>	Mean (SD) Median (IQR) (Range))	Mean (SD) Median (IQR) (Range)	Mean (SD) Median (IQR) (Range)
<b>STAI short form anxiety questionnaire</b>	Mean (SD) Median (IQR) (Range)	Mean (SD) Median (IQR) (Range)	Mean (SD) Median (IQR) (Range)
<b>MARS (For CH group only)</b>	Mean (SD) Median (IQR) (Range)	Mean (SD) Median (IQR) (Range)	Mean (SD) Median (IQR) (Range)

\*The values included here will depend on the data. Number of previous pregnancies that reached at least 24 weeks. This is obtained from the first number in the *pari1\_bl2* variable.

^This information is located in the notes review CRF question 15. There have been some data entry errors regarding the dates for questions 15a and 15b. Some pre randomisation dates have been entered for the post randomisation question and vice versa. The dates entered will therefore need to be compared with the date of randomisation, and categorised as pre- or post-study entry based on this information.

#### TABLE 2: BASELINE CHARACTERISTICS BY RANDOMISED GROUP (CHRONIC HYPERTENSION COHORT)

A replication of dummy Table 1 but for the chronic hypertension group

Add to Appendix:

table: Baseline characteristics for gestational hypertension by entry

A replication of dummy Table 1 but for *de novo* vs. transitioned from BUMP 1, for the gestational hypertension group

### 4.3 DEFINITION OF POPULATION FOR ANALYSIS

All women for whom outcome data are available will be analysed in the group to which they were allocated, irrespective of whether they received that intervention or not. All analyses will be carried out separately for the gestational and chronic hypertension cohorts due to the variation in the timing of their recruitment into the study.

For all neonatal outcomes, the analysis will exclude cases where there was pregnancy loss (for whatever cause) without a live birth before 24 weeks gestation. This information is recorded in question 2 of the notes review (variable *stabeop\_nr*) and those with either miscarriage <24 weeks or termination of pregnancy will be excluded. The option 'termination of pregnancy' in question 2 of the notes review will only include terminations before 24 weeks gestation as anything over this will be recorded as a still birth.

Fidelity to the monitoring schedule will only be measured in the intervention group.

For women that are recruited late into pregnancy, if a delivery occurs before any BPs are measured, a variable will be derived indicating 'delivery before primary outcome recorded' / 'delivery within 2 days of recruitment'. The number of women falling into this category will be reported as they will not have truly missing data and will not be included in the primary outcome analysis.

### 4.4 POOLING OF INVESTIGATIONAL SITES

Randomisation was stratified by recruitment site. Site will be adjusted for in the analysis by including it as a random effect in the statistical models.

### 4.5 DATA MONITORING COMMITTEE AND INTERIM ANALYSES

A DSMC analysis plan and charter have been written in separate documents which are independent of the main statistical analysis plan. There are no plans to stop the trial for efficacy or futility; however, the DSMC has periodically reviewed the accrued data for safety.

## 5 PRIMARY OUTCOME ANALYSIS

The primary objective is to evaluate whether self-monitoring of BP reduces systolic BP in women with hypertension in pregnancy. All analysis will be carried out separately for the gestational and chronic hypertension cohorts.

TABLE 3: DUMMY TABLE FOR PRIMARY OUTCOME (GESTATIONAL HYPERTENSION COHORT)

	USUAL CARE N=	SELF MONITORING N=	OVERALL N=	P-value
Mean (SD) systolic blood pressure				-
Difference in means (95% CI)*				

\* Self-monitoring vs. usual care; estimated from linear mixed effects model adjusting for mean baseline SBP, parity, transfer from BUMP 1 and recruitment site

TABLE 4: DUMMY TABLE FOR PRIMARY OUTCOME (CHRONIC HYPERTENSION COHORT)

	USUAL CARE N=	SELF MONITORING N=	OVERALL N=	P-value
Mean (SD) systolic blood pressure				-
Difference in means (95% CI)*				

\* Self-monitoring vs. usual care; estimated from linear mixed effects model adjusting for mean baseline SBP, parity) and recruitment site

### 5.1 GESTATIONAL HYPERTENSION COHORT

A linear mixed-effects model with an unstructured covariance matrix will be fitted to the outcome of mean systolic blood pressure. The model will include fixed effects for randomised group, parity [pari1\_bl2] (fitted as a binary 0/1 fixed effect indicating null parity vs. any parity), and baseline mean systolic blood pressure. A variable indicating whether the participant transferred from BUMP1 or not will be derived and included as a fixed effect. Site will be included in the model as a random effect.

An adjusted mean difference between the randomised groups, together with a 95% confidence interval and a P value, will be estimated from the model.

### 5.2 CHRONIC HYPERTENSION COHORT

A linear mixed-effects model with an unstructured covariance matrix will be fitted to the outcome of mean systolic blood pressure. The model will include fixed effects for randomised group, binary parity [pari1\_bl2] and baseline mean systolic blood pressure. Site will be included in the model as a random effect.

An adjusted mean difference between the randomised groups, with 95% confidence interval and a P value, will be estimated from the model.

**Note:** as this cohort are all expected to be recruited *de novo*, there will not be an adjustment for transfer from BUMP 1 unless there are women in this group found to be newly diagnosed chronic hypertension cases.

### 5.3 HANDLING MISSING DATA (FOR BOTH THE GESTATIONAL AND CHRONIC HYPERTENSION COHORTS SEPARATELY)

The variables required to derive the primary outcome are all obtained from the notes review. The pattern of missing outcomes with respect to the primary outcome (i.e. notes review unavailable) will be explored by comparing the percentage of missing data between the two randomised arms. Baseline characteristics will be summarised for those participants with a missing primary outcome in order to establish whether they differ from the main cohort. The number of women falling into the category 'delivery before primary outcome recorded' / 'delivery within 2 days of recruitment' will be reported as they will not have truly missing data.

#### 5.4 HANDLING OUTLIERS AND UNREALISTIC DATA

A possible outlier is defined as a data-point three standard deviations from the mean of its distribution. Values of home systolic blood pressure <70mmHg or >260mmHg and/or diastolic blood pressure <40mmHg or >150mmHg are not considered plausible (based on Stergiou, 1998) and will be set to missing. Outliers that have not already been queried in data cleaning will be queried for double-checking at this stage and updated as appropriate. Analysis will proceed by retaining plausible outliers.

#### 5.5 HANDLING MULTI-CENTRE/CLUSTERED DATA

Randomisation was stratified by recruitment site. Site will be adjusted for in the analysis by including it as a random effect in the statistical models.

#### 5.6 MULTIPLE COMPARISONS AND MULTIPLICITY

The protocol clearly states the primary outcome that is to be compared between the 2 randomised groups. Despite separating the analysis for the gestational and chronic hypertension cohorts, only one primary outcome has been specified; therefore, there are no issues of multiple comparisons and multiplicity. No adjustment for multiple testing will be carried out; however, interpretation of significant secondary analyses will be made with caution.

#### 5.7 MODEL ASSUMPTIONS

Model assumptions will be checked for both the GH and CH groups separately. A linear mixed effects model assumes that the errors are uncorrelated and normally distributed. As the errors are estimated by the residuals, these will be graphically assessed to ensure that the model assumptions are met.

## 6 SECONDARY OUTCOMES ANALYSIS

Secondary outcomes are grouped by variable type (Binary/Continuous/Categorical). Analyses will be conducted on all randomised participants and carried out separately for the gestational and chronic hypertension groups.

### 6.1 BINARY OUTCOMES

The following binary outcomes will be analysed separately for the gestational and chronic hypertension cohorts:

- Proportion with healthcare professional-measured systolic blood pressure readings >140mmHg,
- proportion with severe hypertension,
- proportion with pre-eclampsia,
- proportion requiring a blood transfusion,
- Proportion of women with spontaneous onset of labour,
- proportion of stillbirths,
- proportion of early neonatal deaths,
- proportion of infants <10<sup>th</sup> centile for birthweight, and
- proportion of infants admitted to the neonatal unit

Results will be presented as follows:

TABLE 5: DUMMY TABLE FOR BINARY OUTCOMES

	USUAL CARE	SELF MONITORING	OVERALL	ODDS RATIO (95% CI)	P-VALUE
OUTCOME	n (%)	n (%)	n (%)		

\*Self-monitoring vs. usual care; estimated from logistic mixed effects model adjusting for parity and recruitment site

#### 6.1.1.1 GESTATIONAL HYPERTENSION COHORT

A logistic mixed effects model will be fitted to the outcome collected by postnatal review. The model will adjust for parity (as a binary variable) and will include site as a random effect. A variable indicating whether the participant transferred from BUMP1 or not will be derived and also fitted as a fixed effect. Site will be included in the model as a random effect. The treatment effect will be described using an odds ratio with 95% confidence interval and the associated P value will also be presented.

#### 6.1.1.2 CHRONIC HYPERTENSION COHORT

A logistic mixed effects model will be fitted to the outcome collected by postnatal review. The model will adjust for parity (as a binary variable) and will include site as a random effect. Site will be included in the model as a random effect. The treatment effect will be described using an odds ratio with 95% confidence interval and the associated P value will also be presented. Note: as this cohort are all expected to be recruited *de novo*, there will not be an adjustment for transfer from BUMP 1 unless there are women in this group found to be newly diagnosed chronic hypertension cases.

For both the gestational and chronic hypertension cohorts, the analysis of neonatal outcomes (those related to the baby rather than the mother) will account for the potential clustering effect of twins by including a fixed effect indicating twin birth and fitting the models with robust standard errors.



Some of the outcomes are likely to have very small numbers of events, such as maternal deaths, stillbirths, early neonatal deaths and admissions to the neonatal unit. If less than 10% of the women/babies have an event and/or there are less than 5 people in any one cell, the outcome will be presented descriptively.

### 6.1.1.3 DESCRIPTIVE ANALYSIS:

The following outcomes will be presented descriptively (by randomised group and hypertension cohort), with no formal statistical comparison between groups:

- The proportion of women with each of the serious maternal complications listed in section 3.2.7.4,
- the proportion of women who died,
- the proportion of infants <3<sup>rd</sup> centile for birthweight,
- the proportion with DBP>90 mmHg,
- the proportion SBP>140 mmHg AND/OR DBP>90 mmHg,
- the proportion of days with completed home blood pressure readings (fidelity)

## 6.2 CONTINUOUS OUTCOMES

The following continuous secondary outcomes will be analysed separately for the gestational and chronic hypertension cohorts and presented as shown in the table below:

- EQ5D VAS and Index value
- Gestation at delivery
- Length of stay on neonatal unit
- MARS-5
- STAI-6
- Mean clinic measured diastolic blood pressure
- Centile of birthweight

TABLE 6: DUMMY TABLE FOR CONTINUOUS OUTCOMES (CHRONIC HYPERTENSION)

		USUAL CARE	SELF MONITORING	OVERALL
Mean (SD)	Baseline <sup>^</sup>			
Median (IQR)	30 week follow up <sup>^</sup>			
[range]	Postnatal follow up			
	Difference in means (95% CI)* OR medians**			P-VALUE
30 weeks <sup>^</sup>				
Postnatal				

<sup>^</sup>If applicable

\*Self-monitoring vs. usual care; estimated from linear mixed effects model adjusting for parity and recruitment site

\*\*Self-monitoring vs. usual care; estimated from quantile regression adjusting for parity and recruitment site

These continuous secondary outcomes will be analysed as follows:

### 6.2.1.1 GESTATIONAL HYPERTENSION COHORT

A linear mixed-effects model will be fitted to the data with the outcome at postnatal notes review (and 30 week follow up if applicable), as the dependent variable. The model will include a random intercept for each

participant to account for the repeated measures on the same participant (where applicable), as well as a random effect for site. The model will include fixed effects for randomised group, parity (binary) the baseline value of the outcome of interest (where available) and a variable indicating whether the participant transferred from BUMP1 or not. Adjusted mean differences between randomised groups with 95% confidence intervals and P values will be estimated from the model at each applicable time point.

#### 6.2.1.2 CHRONIC HYPERTENSION COHORT

A linear mixed-effects model will be fitted to the data with the outcome at postnatal notes review (and 30 week follow up if applicable), as the dependent variable. The model will include a random intercept for each participant to account for the repeated measures on the same participant (where applicable), as well as a random effect for site. Included in the model will be fixed effects for randomised group, parity (binary), the baseline value of the outcome of interest (where available) and a term for the treatment by visit interaction to allow the treatment effect to be estimated at each time point. Adjusted mean differences between randomised groups with 95% confidence intervals and P values will be estimated from the model at each applicable time point.

**Note:** as this cohort are all expected to be recruited *de novo*, there will not be an adjustment for transfer from BUMP 1 unless there are women in this group found to be newly diagnosed chronic hypertension cases.

For both cohorts above, it is likely that length of stay on the neonatal unit and gestation at delivery will be highly skewed. If this is the case then the median (IQR, range) in each randomised group will be presented with the difference in medians and 95% confidence interval. If appropriate, the groups will be compared using quantile regression, adjusting for the same covariates as stated in the two sections above.

The analysis of neonatal outcomes (those related to the baby rather than the mother) will account for the potential clustering effect of twins by including a fixed effect indicating twin birth and fitting the models with robust standard errors.

#### 6.2.1.3 AREA UNDER THE CURVE OVER TIME

AUC will be analysed using a mixed-effects model with fixed effects for randomised group, parity (binary) and baseline blood pressure and a random effect for site. Adjusted mean differences between randomised groups with a 95% confidence interval and P value will be estimated from the models. If the AUC data are not normally distributed, an appropriate non-parametric alternative will be considered (e.g. quantile regression)

#### 6.2.1.4 Descriptive analysis

The following continuous outcomes will be presented descriptively (by randomised group and hypertension cohort) using mean, standard deviation, median, interquartile range and range with no formal statistical comparison between groups unless specified elsewhere:

- Birthweight
- The percentage of expected home blood pressure readings (fidelity)

### 6.3 CATEGORICAL OUTCOMES

#### 6.3.1 MODE OF DELIVERY, ONSET OF LABOUR AND INDICATION FOR INDUCTION OF LABOUR OR PRE-LABOUR CAESAREAN SECTION

The categorical outcomes below will be summarised descriptively, with the proportion in each category. There will be no statistical analysis comparing randomised groups:

- Mode of delivery
- Onset of labour [onslab\_nr]
- Indication for induction of labour or pre-labour caesarean section [indicat\_nr]

The dummy table below will be replicated to present summary statistics separately for the gestational and chronic hypertension cohorts.

**TABLE 7: DUMMY TABLE FOR CATEGORICAL OUTCOMES**

	<b>USUAL CARE</b>	<b>SELF MONITORING</b>
	<b>N(%)</b>	<b>N(%)</b>
<b>Mode of delivery</b> 1=Spontaneous vaginal delivery 2=Assisted vaginal delivery 3=Emergency pre-labour caesarean section 4=Emergency caesarean section in labour 5=Elective pre-labour caesarean section		
<b>Onset of Labour</b> 1=Spontaneous 2=Induction 3=Pre-labour caesarean section 4=Pre-labour rupture of membranes/stimulation of labour		
<b>Indication for induction of labour or pre-labour CS*</b> 1=Pre-eclampsia 2=Chronic hypertension only 3=Gestational hypertension only 4=Other medical complication 5=Reaching 37 weeks gestation		

6=Maternal hypertension not controlled by maximal therapy		
7=Maternal haematological abnormality		
8=Maternal biochemical abnormality		
9=Fetal concern on ultrasound scan		
10=Fetal compromise on cardiotocography		
11=Severe maternal symptoms		
12=Preterm prelabour rupture of membranes		
13=Antepartum haemorrhage		
14=Fetal growth restriction		
15=Other		
16=Missing		

\*Women can have one or more of these. The denominator is the number of women with either induction or pre-labour caesarean section as the response to question 3 of the notes review

### 6.3.2 ADAPTED BELIEFS ABOUT MEDICINES QUESTIONNAIRE

(Postnatal and 30 week follow up)

The (original) Beliefs About Medicines questionnaire (BMQ-Specific) is a 10-item tool assessing participant views about their prescribed medications and medicines in general. It is assessed using a 5 point Likert scale (strongly agree=5 to strongly disagree=1).

As the BMQ-S has been shortened to 8 statements for use this study and is not validated in this form, it cannot be meaningfully scored and assessed in the same way that the 10-item validated tool would be. Thus, item responses will be summarised descriptively and presented graphically using divergent stacked bar graphs, separately for each randomised group, for each hypertension cohort, at each of the time points of measurement.

### 6.3.3 SELF-EFFICACY QUESTIONNAIRE ASSESSING HEALTH BEHAVIOUR

(Baseline, 30-week follow up and postnatal follow up)

The (original) Brief-IPQ is a 9-item tool in which each item assess one dimension of illness perception. The response for each item is a number between 0 and 10. The meaning of the value varies depending on the question but, 0 indicates either not at all sure, no understanding, no control or no concern and 10 indicates either very sure, very clear understanding, extreme amount of control or extreme concern.

In this study, four of the original nine items are used, and two new ones are added. In this form, the items cannot be scored according to the rules for the original tool; thus, the responses to this questionnaire will be summarised descriptively for each item, separately for each randomised group and hypertension cohort, at each of the time points of measurement.

## 7 SENSITIVITY ANALYSIS

If outliers are identified, a sensitivity analysis excluding these outliers will be carried out to determine the impact of these observations on the treatment effect of the primary outcome.

As a sensitivity analyses of the primary outcome:

- Baseline covariates found to be predictive of missingness will be included as main effects in the linear mixed effects models for the two hypertension cohorts.
- A sensitivity will be carried out removing all inpatient readings; thus using just average clinic-measured SBP readings.
- A sensitivity will be carried out using the highest clinic measurement rather than the average clinic-measured SBP readings.
- A sensitivity analysis will be carried out on the combined CH & GH cohorts in an IPD type analysis (ie all women in BUMP2 regardless of CH or GH plus whether de novo or transitioned).

The need for MI was considered and it was decided that it was not necessary as there is at least 95% data completeness for the primary outcome.

## 8 SUBGROUP ANALYSES

A subgroup analysis will be carried out for women recruited *de novo* into the study vs. those that transitioned from BUMP 1 by including an interaction of this binary indicator variable with the randomisation group in the model for the primary outcome analysis. This will only be done for the gestational hypertension group as no women transitioning from BUMP 1 are expected to have chronic hypertension.

Other sub group analyses (both within GH and CH) include:

- Parity: 0 vs 1 or more
- Gestational age at entry
  - o for GH <34/40 vs ≥34/40
  - o for CH <12, 12 to 19+6, ≥20
- Previous self-measurement of blood pressure in this pregnancy: yes vs no [*bpmeas\_b12*] (on baseline CRF)– Y/N]
- Deprivation score (IMD - use postcode from baseline CRF [*postco\_b12*])
- Ethnicity [*ethnic\_b12*]: White Irish/British vs. others
- Highest qualification [*edlevel\_b12*]: PG and above vs. 1<sup>st</sup> degree/prof quals vs. all the rest

## 9 SAFETY ANALYSIS

All randomised participants will be included in the safety analysis.

All serious adverse events (SAE) occurring during the trial shall be detailed and reported by randomisation group and hypertension cohort. The overall incidence of women experiencing at least one SAE will be compared between the randomised groups using a Chi squared test (or Fisher's exact test in the case of small numbers) and the difference in proportions with 95% confidence intervals will be presented. The total number of SAEs per group will also be presented.

Only adverse events that are clinically judged (by the supervising site PI) as being caused by the trial intervention will be reported to the PC-CTU. These will be summarised and analysed in the same way as the serious adverse events.

TABLE 8: DUMMY TABLES FOR SAFETY OUTCOMES

Participant ID	Intervention Arm	Description of SAE	Related to intervention (yes/no)	Severity*	Expected (yes/no)

\*mild, moderate or severe

	USUAL CARE	SELF-MONITORING	OVERALL
<b>Number of SAEs</b>			
<b>Number of participants experiencing at least one SAE</b>	<b>N(%)</b>	<b>N(%)</b>	<b>N(%)</b>
<b>Difference in proportions, 95% C.I</b>			
<b>Test for difference in proportions (<math>\chi^2</math>(df), p-value)</b>			

	USUAL CARE	SELF-MONITORING	OVERALL
<b>Number of AE*s</b>			
<b>Number of participants experiencing at least one AE*</b>	<b>N(%)</b>	<b>N(%)</b>	<b>N(%)</b>
<b>Difference in proportions, 95% C.I</b>			
<b>Test for difference in proportions (<math>\chi^2</math>(df), p-value)</b>			

\*clinically judged to be caused by the trial intervention

## 10 VALIDATION

A Senior Trial Statistician (or appropriately qualified delegate) will validate the primary and safety analyses.

## 11 CHANGES TO THE PROTOCOL OR PREVIOUS VERSIONS OF SAP

The protocol did not specify splitting the analyses by hypertension cohort. This was decided later following analysis of the OPTIMUM pilot study as the two hypertension cohorts were sufficiently different due to entering the study at different points in their gestation, and therefore having differential exposure to the intervention.

Placental abruption was defined as an outcome in the protocol. However, this was not collected and is therefore not available for analysis.

The protocol states onset of labour and mode of delivery as outcomes, but not specifically comparing spontaneous onset of labour to any other option, or spontaneous vaginal delivery to any other option. This was specified prior to data lock.

The Sensitivity and Subgroup analyses were not specified in the protocol but were specified prior to data lock.

## 12 REFERENCES

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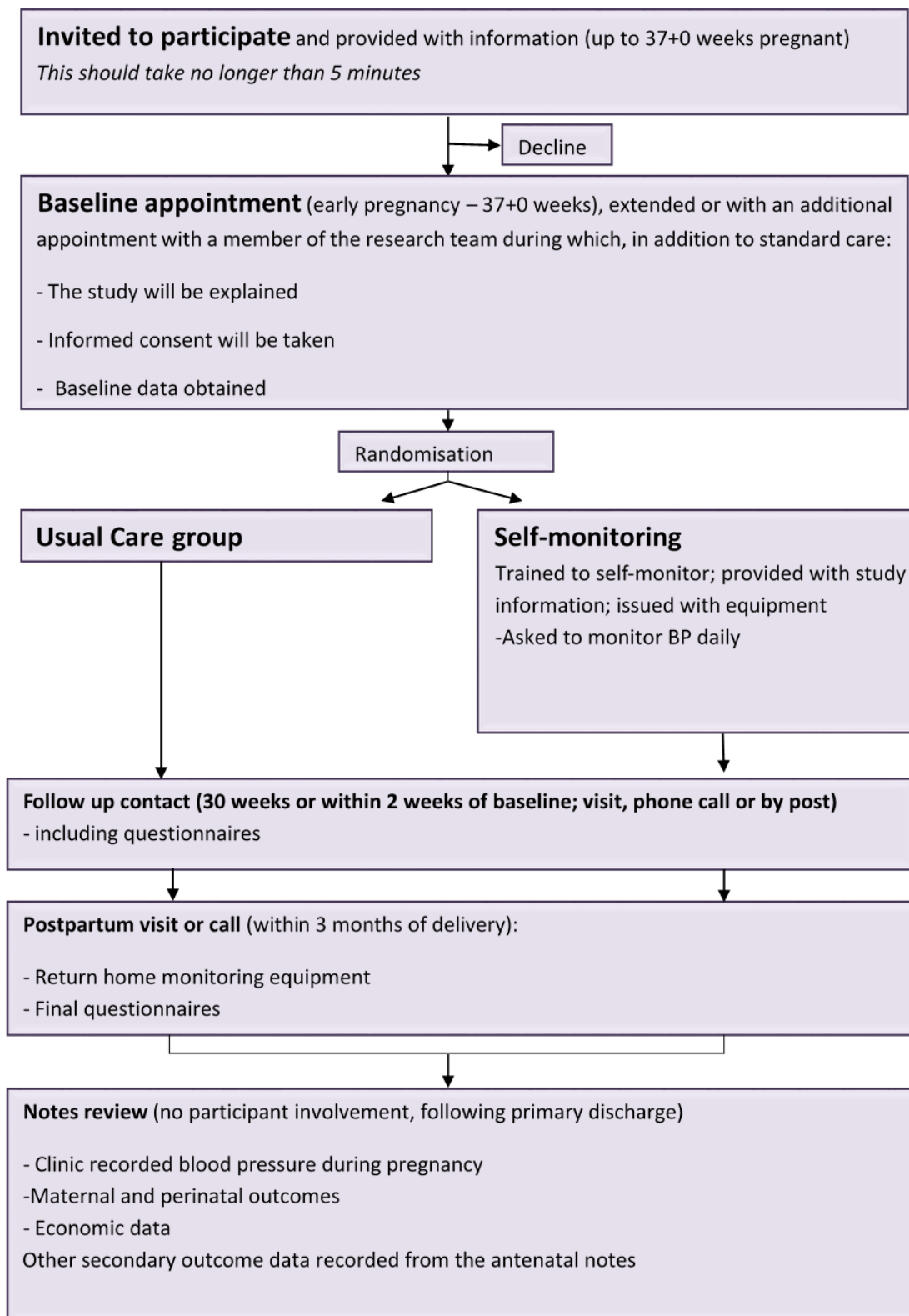
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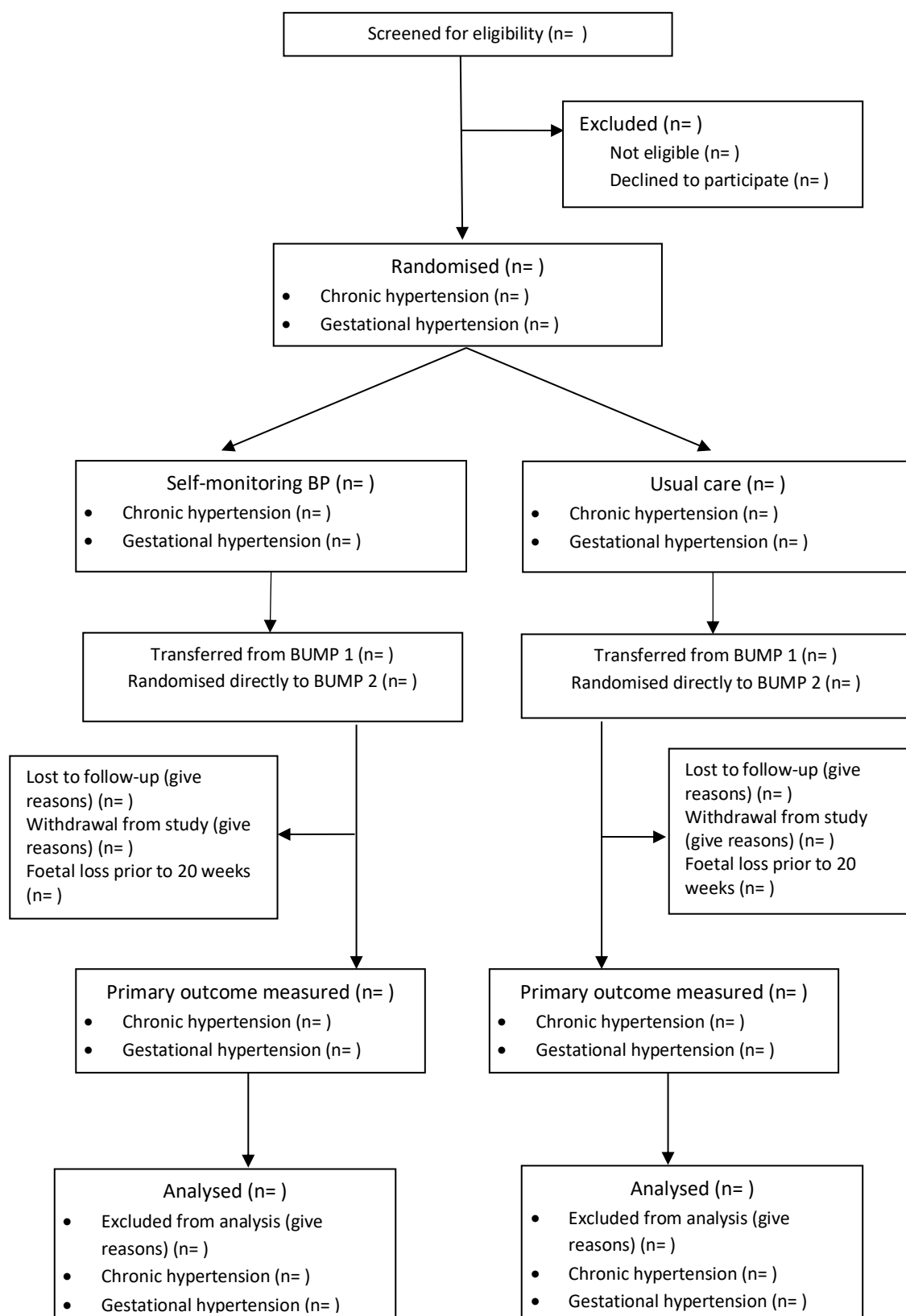
## 13 APPENDICES

### 13.1 APPENDIX I: STUDY FLOW CHART BUMP 2 FOR WOMEN NOT PREVIOUSLY RANDOMISED IN BUMP 1





### 13.2 APPENDIX II. FLOW DIAGRAM OF TRIAL PARTICIPANTS



### 13.3 APPENDIX III. SITE LIST BY CODE

List of current site codes (as determined by the middle section of the Patient ID) and corresponding site names:

Site codes for each site	Site name
003	Barts
013	Birmingham Women's NHS Foundation Trust
006	Chelsea & Westminster
014	Croydon University Hospital
002	GSTT
009	King's College Hospital
011	Kingston
007	Manchester
001	Oxford University Hospitals
005	Royal Berkshire
012	St George's
015	Stoke Mandeville Hospital
010	West Middlesex
008	Whipps Cross
004	Wolverhampton