Primary Care Clinical Trials Unit

STATISTICAL ANALYSIS PLAN

BUMP 1

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

Version 1.0

15th September 2020

Based on version 5.0 of Protocol (3rd June 2020)

	NAME	TITLE	SIGNATURE	DATE
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Version History

Version:	Version Date:	Changes:
0.1	10th January 2019	First version
0.2	3rd April 2019	Updates to derivation of outcomes following meeting with Richard McManus and Greig Dougall
0.3	7th May 2019	Updates following email received from Lucy Chappell 30.4.19

		(stored K:\CV_R\Big BuMP\STATS\2. Stats Plan and Sample Size\SAP\BUMP 1) % of women with severe hypertension (secondary outcome) does not have to be sustained (2 readings) as it does for the primary outcome. Addition of subgroup analyses Updated analysis section with variable names
0.4	20th August 2019	Updates following meeting with Lucy Chappel and Richard McManus – clarifying secondary outcomes and subgroup analyses
0.5	3rd September 2019	Updates following meeting with Lucy Chappel and Richard McManus including: Clarifying per protocol analysis Additional subgroup analysis and removal of site subgroup analysis Addition of secondary outcomes – mean blood pressure and indication for IOL or pre labour CS Replace 'patient' with 'woman' Include mean, SD, median, IQR and range for all continuous outcomes
0.6	17th September 2019	
0.7	15th October 2019	Changes following responses to queries from Richard McManus on previous version. Move health behaviours questionnaires from continuous to categorical and describe in

		more detail the brief illness perception and beliefs about medicines questionnaires
0.8	16th October 2019	Changes following meeting with LMY. Amended description of analysis of primary outcome and subgroup analyses. Section 5.2.1 changed cut off for descriptive analysis from 10% to 2% Clarification of exclusions for neonatal outcomes
0.9	23rd January 2020	Reorganisation of document to include a separate section on derivation of variables. Added rule for coding primary outcome as missing
0.10	24th June 2020	Minor amendments of typos/references before final review
0.11	29th July 2020	Addition of subgroup analyses following meeting with RM, LC, LMY, JM, NW and UG
0.12	9th September 2020	Updates made following review from LMY. Addition of 2 part mixture model instead of hurdle. Addition of MI for missing primary outcome data Change analysis of binary outcomes from logistic to poisson regression.
1.0	15th September 2020	Previous version to version 1.0 and signed off

TABLE OF CONTENTS

1 INTRODUCTION

1.1 PREFACE

Trial statistician: Ly-Mee Yu

Chief Investigator: Richard McManus

Trial Manager: Greig Dougall

This SAP supports version 5.0 of the protocol dated 3rd June 2020. This SAP relates to the BUMP 1 section of the protocol only. A separate SAP has been prepared for the BUMP 2 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 reduces the time to detection of raised blood pressure in pregnancy 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 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. BP can rise rapidly in pregnancy and hypertension may go undetected in between antenatal visits, despite the current extra monitoring in place. 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 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 hypertensio. 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.

1.4 OBJECTIVES

The primary objective is to evaluate whether self-monitoring of BP can detect raised BP earlier than usual care during pregnancy.

The secondary objectives are as follows:

1. To evaluate the effect of self-monitoring of BP in higher risk pregnancy on maternal and perinatal adverse outcomes.

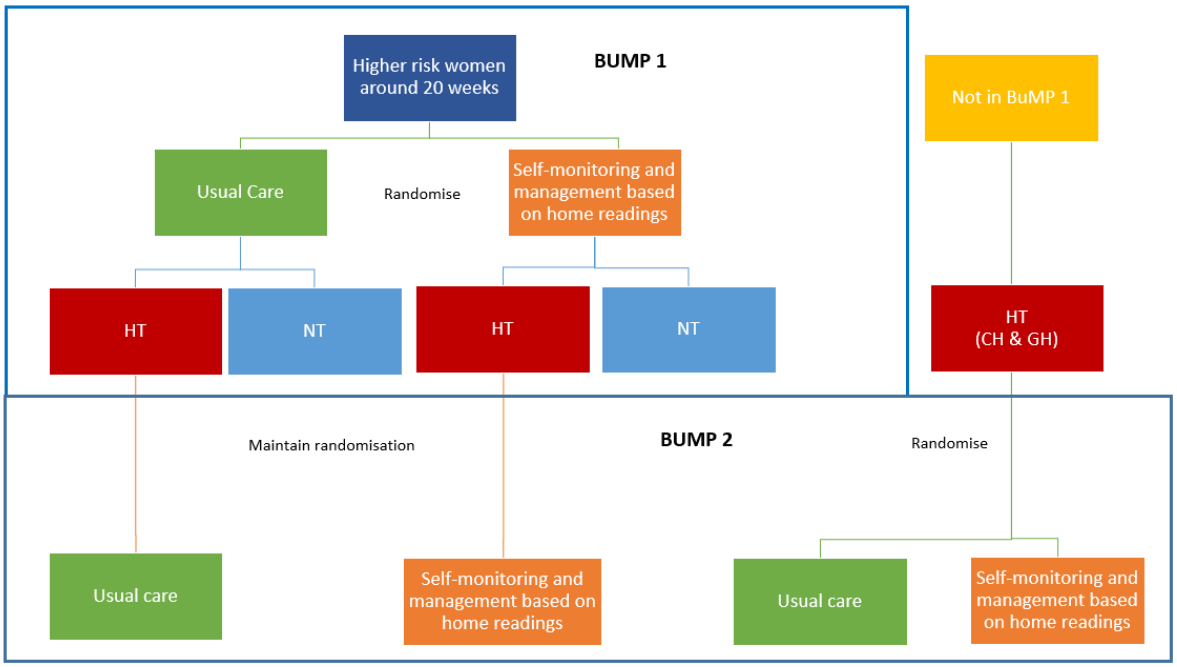
2. To evaluate whether self-monitoring of BP in higher risk pregnancy affects quality of life and is cost effective.
3. To evaluate how self-monitoring of BP in higher risk pregnancy is implemented in daily life and routine clinical practice.

2 TRIAL DESIGN

BUMP 1 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 those defined as being at a higher risk of pre-eclampsia (see inclusion criteria). If a participating woman develops pregnancy hypertension then they will be able to transfer to BUMP 2. The planned sample size is 2262.

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

2.1.1 PRIMARY OUTCOME

The primary outcome is the time to recording of raised BP/onset of hypertension, as measured by a health care professional. This will be established by means of a notes review, carried out following primary discharge. A full description of how the primary outcome will be derived can be found in section 3.1.

2.1.2 SECONDARY OUTCOMES

With the exception of EQ-5D-5L, STAI and health behaviours questions, all secondary outcomes will be established from a notes review, which will take place following primary discharge. EQ-5D-5L, STAI and health behaviours questions will be measured at baseline, follow up (around 30 weeks) and 8 weeks postpartum.

The following are maternal outcomes and relate to secondary objective 1.

- Number and proportion of women with severe hypertension (systolic BP≥160mmHg and/or diastolic BP≥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(creatinine≥90mmol)
    - Eclampsia
    - HELLP syndrome (haemolysis, elevated liver enzymes, low platelets)
    - Liver involvement (ALT or AST >70 U/L)
    - Haematological involvement (platelets <x100^9/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 (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, 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, other)
- Mean clinic measured systolic blood pressure between randomisation and delivery or reaching definition for primary outcome
- Mean clinic measured diastolic blood pressure between randomisation and delivery or reaching definition for primary outcome
- Quality of Life (EQ-5D-5L)(Index value and VAS)

The following are perinatal outcomes and relate to secondary objective 1.

- Number and proportion of stillbirths
- Number and proportion of early neonatal deaths (within 7 days of delivery)
- 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 <10th centile for birthweight
- Number and proportion of infants <3rd 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 objective 2.

- Adapted beliefs about medicines questionnaire
- Adapted brief illness perception questionnaire
- Fidelity to monitoring schedule (% of expected readings and proportion with at least 90% of expected readings)
- STAI-6 short form anxiety questionnaire

2.2 TARGET POPULATION

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)

Exclusion criteria

- Chronic hypertension

2.3 SAMPLE SIZE

A sample size of 2262 (1131/group) assuming a 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, 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.

2.4 RANDOMISATION AND BLINDING IN THE ANALYSIS STAGE

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 (0 or ≥1).

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.

3 DERIVATION OF VARIABLES

3.1 PRIMARY OUTCOME

Variables required

The variables required to derive the primary outcome are from the notes review CRF.

The following questions are required to determine whether the participant was prescribed an anti-hypertensive medication at any point after randomisation:

6a, 6b and 6c. Each anti-hypertensive drug prescribed will be listed as a separate variable in the database, along with a variable indicating the date on which it was first prescribed. There will be a set of variables relating to prescribed drugs for each of 20 weeks (question 6a of notes review), 30 weeks (question 6b of notes review) and the week prior to delivery/end of pregnancy (question 6c of the notes review). The variable names for the dates are as follows:

wk20date[01-10]_nr

wk30date[01-10]_nr

eopdate[01-10]_nr

The 20 week variable is intended to be the pre randomisation variable. However, the dates will be compared to the date of randomisation and only included in the primary outcome if they are post randomisation.

The following questions are required to determine whether the participant had a raised BP at any point after randomisation:

15a, 15b, 16 and 17. These questions contain the blood pressure readings pre randomisation (15a), post randomisation (15b), DAU/MAU BP readings post randomisation (16) and the highest blood pressure readings on each day of a ward admission (17). 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. It has therefore been decided to compare the dates entered with the date of randomisation, and categorise as pre or post randomisation based on this information.

The date variables and associated blood pressure variables are:

Notes review question	Date	1st BP reading	2nd BP reading	3rd BP reading
15a (pre randomisation)	pcbpdat_nr	pcbpfsys_nr pcbpfdia_nr	pcbpssys_nr pcbpsdia_nr	pcbptsys_nr pcbptdia_nr
15b (each clinic visit - up to 75)	cbpdat[01-75]_nr	cbpfsys[01-75]_nr cbpfdia[01-75]_nr	cbpssys[01-75]_nr cbpsdia[01-75]_nr	cbptsys[01-75]_nr cbptdia[01-75]_nr

16 (each DAU/MAU visit – up to 75)	dbpdat[01-75]_nr	dbpfsys[01-75]_nr dbpfdia[01-75]_nr	dbpssys[01-75]_nr dbpsdia[01-75]_nr	dbptsys[01-75]_nr dbptdia[01-75]_nr
17 (each ward admission – up to 100)		Highest SBP	Highest DBP	
	wbpdat[001-100]_nr	whsbp[001-100]_nr	whdbp[001-100]_nr	

Derivation

The woman is defined as having raised blood pressure/hypertension if either of the following are true:

1. Sustained systolic BP ≥140 and/or diastolic BP ≥90 mm Hg from any community or hospital setting recorded (post randomisation) in the notes review. For sustained, at least two high readings within 1 week (date of first raised BP + 6 days) 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.

Or

2. The woman has received a new prescription of antihypertensive medication for raised blood pressure (in order to capture diagnoses where two raised blood pressures have not been recorded in the notes review for whatever reason).

The time to onset of hypertension will be defined as the difference between the date of randomisation and the earliest date recorded for either of the above 2 events. In the first case, the 'earliest date recorded' will be for the second of the 2 high readings within 1 week. For the second case, the earliest date of prescription will be listed as the date of diagnosis. If a participant has both events then the date of the earliest one will be used for the primary outcome.

The primary outcome will be coded as missing if the notes review has not been completed (i.e. participant is lost to follow up or has withdrawn) or, if the notes review has been completed, but there are ≤1 post randomisation clinic, DAU/MAU or ward admission blood pressure measurements recorded in the notes review AND no post randomisation prescription for an anti-hypertensive drug.

For the purposes of the primary analysis, the time to onset of hypertension will be set to zero for all participants who did not have an onset of hypertension during the study period and who have not been coded as missing as per the previous rule.

3.2 Secondary outcomes - Binary

3.2.1 Percentage of women with severe hypertension

Severe hypertension is defined as systolic BP≥160mmHg and/or diastolic BP≥110mmHg from any community of hospital setting recorded (post randomisation) in the notes review. This will be derived in the same way as for part one of the primary outcome (without doing the time to severe hypertension or prescribing of anti-hypertensive medication and without having to be sustained (i.e. 1 high reading is sufficient)) but with cut offs of 160mmHg for systolic BP and 110mmHg for diastolic BP.

3.2.2 Percentage of women with pre-eclampsia

The proportion of women with pre-eclampsia will be calculated from question 7 of the notes review CRF. The woman has pre-eclampsia if diagnote1_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 was not diagnosed with pre-eclampsia.

3.2.3 Percentage of women with serious maternal complications

The proportion of women with each of the following serious maternal complications will be calculated from question 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.

- 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≥90mmol) (pdrenal_nr=1)
- Haematological involvement (platelets <x100^9/L) (prhaem_nr=1)

3.2.4 Percentage of women experiencing one or more serious maternal complication

The percentage of women experiencing one or more serious maternal complication listed in Section 3.2.3 will be calculated. The woman will be classified as having at least one serious maternal complication if any of the variables specified in Section 3.2.3 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.

3.2.5 Percentage 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 (i.e. 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.

3.2.6 Percentage 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. 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.

3.2.7 Percentage 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 options will be classed as not having a spontaneous onset of labour ('onslab_nr' = 2, 3 or 4).

3.2.8 Percentage of stillbirths

Information about still births is recorded in question 2 of the notes review. A baby is recorded as having been still born 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 also be required for twin pregnancies.

3.2.9 Percentage of early neonatal deaths

An early neonatal death is defined as one occurring within 7 days of delivery. Question 14 of the notes review indicates whether the baby died prior to discharge (outcob1_nr). If the baby died (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 also be required for twin pregnancies.

3.2.10 Percentage of babies small for gestational age (<10TH and <3RD 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-21st 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 sex will be set to female and a description of how many babies this applied to will be given.

The variables 'weight2_nr' and 'sex2_nr' will also be required for twin pregnancies.

3.2.11 Percentage 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.

3.2.12 Percentage 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.

3.2.13 Fidelity - Percentage of women with at least 90% of expected home blood pressure readings

This data is only applicable to the intervention group. The proportion of women who have completed ≥90% of expected home blood pressure readings between randomisation and the first of pregnancy loss, delivery, or diagnosis of raised blood pressure according to the definition used for the primary outcome will be calculated. A woman is expected to complete 3 home blood pressure readings each week unless her blood pressure rises

above 135/85, in which case she is prompted to do a reading every day. The fidelity data will be obtained from the tele-monitoring dataset,

3.3 Secondary outcomes – Continuous

3.3.1 Mean clinic measured systolic blood pressure

The mean clinic measured systolic blood pressure between randomisation and the day before delivery or reaching definition for primary outcome (whichever is first) will be calculated for each woman.

Questions 15a, 15b, 16 and 17 of the notes review contain all the clinic measured blood pressures. These questions contain the blood pressure readings pre randomisation (15a), post randomisation (15b), DAU/MAU BP readings post randomisation (16) and the highest blood pressure readings on each day of a ward admission (17). 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. It has therefore been decided to compare the dates entered with the date of randomisation, and categorise as pre or post randomisation based on this information. See section 3.1 for BP and date variable names.

3.3.2 Mean clinic measured diastolic blood pressure

The mean clinic measured diastolic blood pressure between randomisation and the day before delivery or reaching definition for primary outcome (whichever is first) will be calculated for each woman.

This will be done in the same way as for systolic blood pressure, detailed in section 3.3.1.

3.3.3 EQ5D VAS and Index value

The EQ-5D-5L 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.

3.3.4 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.

3.3.5 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 also be required for twin pregnancies.

3.3.6 BIRTH WEIGHT CENTILE

The birthweight centile for each baby will be calculated as described in section 3.2.10.

3.3.7 LENGTH OF STAY ON NEONATAL UNIT

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.

3.3.8 FIDELITY TO MONITORING SCHEDULE

This data is only applicable to the intervention group. The percentage of expected home blood pressure readings will be calculated for each woman. A woman is expected to complete 3 home blood pressure readings each week unless her blood pressure rises above 135/85, in which case she is prompted to do a reading every day. The number of readings carried out between randomisation and the first of pregnancy loss, delivery, or diagnosis of raised blood pressure according to the definition used for the primary outcome will be calculated. The percentage of expected readings will be calculated as

(Number of readings carried out/Number of expected readings) x 100

The fidelity data will be obtained from the tele-monitoring dataset.

3.3.9 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' = 0 to 'very much' =3. The scores need to be recoded as 1-4 ('not at all'=1 to 'very much'=4) and 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 across the 6 items is obtained and can range from 6 to 24. These are scaled to be out of 100 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_bl1	calm_fu	calm_pfu
I am tense	tense_bl1	tense_fu	tense_pfu
I feel upset	upset_bl1	upset_fu	upset_pfu
I feel relaxed	relax_bl1	relax_fu	relax_pfu
I feel content	cont_bl1	cont_fu	cont_pfu

I am worried	worri_bl1	worri_fu	worri_pfu

3.4 SECONDARY OUTCOMES – CATEGORICAL

3.4.1 ONSET OF LABOUR

Onset of labour is recorded in the variable 'onslab_nr' and is split into 4 categories as follows:

1 = Spontaneous

2 = Induction

3 = Pre-labour caesarean section

4 = Pre-labour rupture of membranes/stimulation of labour

3.4.2 MODE OF DELIVERY

Mode of delivery is recorded in the variable 'mode_nr' and is split into 5 categories as follows:

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

The variable 'mode2_nr' will also be required for twin pregnancies.

3.4.3 INDICATION FOR INDUCTION OF LABOUR OR PRE-LABOUR CAESAREAN SECTION

Indication for induction of labour or pre-labour caesarean section is recorded in the variables 'indicat_nr__[1-16]'. There are 16 variables as listed below, and a woman can have one or more of these.

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 pre labour rupture of membranes

13 = Antepartum haemorrhage

14 = Fetal growth restriction

15 = Other

16 = Missing

3.4.4 Adapted Beliefs About Medicines Questionnaire

This has been administered at baseline, 30 week follow up and postnatal follow up. It consists of 8 statements related to the woman's views about medicines prescribed and medicines in general. Each statement can be given one of the following 5 responses:

- Strongly agree
- Agree
- Uncertain
- Disagree
- Strongly disagree

3.4.5 Adapted Brief Illness Perception Questionnaire

This has been administered at baseline, 30 week follow up and postnatal follow up. It consists of 6 questions where the response can be recorded as 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.

4 Analysis – General considerations

4.1 Descriptive statistics

Continuous variables will be presented as means with standard deviations and medians with interquartile ranges and ranges 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 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.

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.

Frequencies and percentages will be reported for categorical variables. Continuous variables will be presented using mean, standard deviation, median, interquartile range and range. Number with missing data for each characteristic will 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.

Participant flow from screening through randomisation, follow up and analysis will be presented in a CONSORT flow chart (Appendix II). Note that some women with pregnancy loss have been incorrectly recorded as discontinuations. This is not the case and the pregnancy loss is an outcome as well as the point they are censored.

TABLE 1: BASELINE CHARACTERISTICS BY RANDOMISED GROUP

	USUAL CARE N=	**SELF MONITORING N=**	**OVERALL N N=**
Age (years)	**Mean (SD) Median (IQR) (Range)**	**Mean (SD) Median (IQR) (Range)**	**Mean (SD) Median (IQR) (Range)**
Gestation (weeks)	**Mean (SD) Median (IQR) (Range)**	**Mean (SD) Median (IQR) (Range)**	**Mean (SD) Median (IQR) (Range)**
Parity* 0 1 2 3 4 5 >5	**N(%)**	**N(%)**	**N(%)**
BMI(kg/m^2)	**Mean (SD) Median (IQR) (Range)**	**Mean (SD) Median (IQR) (Range)**	**Mean (SD) Median (IQR) (Range)**
Pregnancy interval >10 years	**N(%)**	**N(%)**	**N(%)**
Family history of pre-eclampsia	**N(%)**	**N(%)**	**N(%)**
Previous history of gestation hypertension or pre-eclampsia	**N(%)**	**N(%)**	**N(%)**
Chronic kidney disease	**N(%)**	**N(%)**	**N(%)**
Twin pregnancy	**N(%)**	**N(%)**	**N(%)**
Diabetes	**N(%)**	**N(%)**	**N(%)**
Autoimmune disease	**N(%)**	**N(%)**	**N(%)**
Current smoker	**N(%)**	**N(%)**	**N(%)**
Ethnic group: Asian or Asian British Black or Black British Chinese	**N(%)**	**N(%)**	**N(%)**

Mixed White British White Irish Other			
Highest qualification: 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(%)**
Mean blood pressure at last clinic visit prior to randomisation^: Systolic Diastolic	**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)**
EQ5D VAS	**Mean (SD)** **Median (IQR)** **(Range)**	**Mean (SD)** **Median (IQR)** **(Range)**	**Mean (SD)** **Median (IQR)** **(Range)**
EQ5D Index Value	**Mean (SD)** **Median (IQR)** **(Range)**	**Mean (SD)** **Median (IQR)** **(Range)**	**Mean (SD)** **Median (IQR)** **(Range)**
STAI short form anxiety questionnaire	**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 variable ''pari1_bl1'.

^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 randomisation based on this information.

4.3 DEFINITION OF POPULATION FOR ANALYSIS

All data will be included in the analysis as far as possible to allow full intention to treat (ITT) analysis. Women will be analysed in the groups they were allocated, irrespective of whether they received that intervention or not. 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.

A second analysis will be carried out based on the per protocol population. For the usual care group this will be all women for whom a notes review has been carried out. For the self-monitoring group this will include all women who have completed ≥90% of expected home blood pressure readings between randomisation and the first of pregnancy loss, delivery, or diagnosis of raised blood pressure according to the definition used for the primary outcome.

4.4 POOLING OF INVESTIGATIONAL SITES

Randomisation was stratified by recruitment site. Site will be explored to determine whether it needs to be included in the models as a random effect. If so then all models will adjust for site as a random effect. If not then a fixed effect will be used.

4.5 DATA MONITORING COMMITTEE AND INTERIM ANALYSES

Interim analyses for safety will be conducted for this trial. 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 will review the accrued data for safety. All interim analyses will be descriptive and there will be no formal comparisons between groups.

5 PRIMARY OUTCOME ANALYSIS

The primary objective is to determine whether self-monitoring of blood pressure in pregnancy can detect raised blood pressure/onset of hypertension earlier than usual care.

TABLE 2: DUMMY TABLE FOR PRIMARY OUTCOME

	USUAL CARE	SELF MONITORING	OVERALL
Number (%) of participants with raised blood pressure			
Mean (SD) time to raised blood pressure			
Median (IQR) [range] time to raised blood pressure			

Treatment (Self-monitoring versus usual care)[1]	COEFFICIENT	95% LOWER C.I.	95% UPPER C.I.	P-VALUE
Raised blood pressure[2] **Time to raised blood pressure[3]**				

*This table is an example only and will differ depending on the exact model used

1. Adjusted for parity and recruitment site
2. Estimated from the first stage of the hurdle model (probit)
3. Estimated from the second stage of the hurdle model (linear regression)

The primary outcome is the time to recording of raised BP/onset of hypertension, as measured by a health care professional. This will be established by means of a notes review, carried out following primary discharge. This outcome will be derived from variables recorded in the notes review case report forms.

The primary outcome will be analysed using a method that accounts for both women who did not experience any raised BP and those with number of days to raised BP from randomisation, such as a two-part mixture model (e.g. hurdle model or Tobit model). The first stage of the model determines whether the woman clears

the hurdle (in this case, diagnosis of hypertension). The second stage determines the value of the outcome conditional on having cleared the hurdle (in this case, the time to diagnosis of hypertension, conditional on having been diagnosed). The model will include group and parity (0 or ≥1) as fixed effects and site as a random or fixed effect depending on the results of the preliminary exploration of site.

Parity is recorded in the variable 'pari1_bl1' in the dataset.

5.1 HANDLING MISSING DATA

The variables required to derive the primary outcome are all obtained from the notes review. There should be very little missing data on variables used to define the primary outcome after review unless the notes are unavailable.

The availability of the outcome data for the primary outcome will be summarised by randomised group. Logistic regression models will explore any association between baseline characteristics and availability of the primary outcome. Missing primary outcome data will be reported overall and by randomised group. Covariates found to be predictive of missingness (P< 0.05) will be included in the analysis model in a sensitivity analysis of the primary outcome.

A sensitivity analysis will be conducted to assess the potential impact of bias due to missing data on the primary outcome. An ITT analysis will be conducted and multiple imputation will be used to replace the missing data with plausible values. As Multiple Imputation (MI) is valid under a missing at random (MAR) assumption, the MI model will include any variables that have been identified as predictive of missingness and any variables that are to be included in the analysis model. The primary analysis model will then be rerun with the imputed missing outcome.

5.2 HANDLING OUTLIERS

A possible outlier is defined as a data-point three standard deviations from the mean of its distribution and/or systolic blood pressure <70mmHg or >260mmHg and/or diastolic blood pressure <40mmHg or >150mmHg. For outliers that have not already been queried in data cleaning, they will be queried for double-checking at this stage and updated as appropriate. Analysis will proceed by retaining plausible outliers. Values of systolic blood pressure <70mmHg or >260mmHg and diastolic blood pressure <40mmHg or >150mmHg are not considered plausible other than in emergency settings not relevant to our analysis and will be set to missing.

5.3 HANDLING MULTI-CENTRE/CLUSTERED DATA

Randomisation was stratified by recruitment site. Site will be explored to determine whether it needs to be included in the models as a random effect. If so then all models will adjust for site as a random effect. If not then a fixed effect will be used.

5.4 MULTIPLE COMPARISONS AND MULTIPLICITY

The protocol clearly states the primary outcome that is to be compared between the 2 randomised groups. Only one primary outcome has been specified in a two-arm trial, therefore there are no issues of multiple comparisons and multiplicity. Interpretation of significant secondary analyses will be made with caution.

5.5 MODEL ASSUMPTIONS

Hurdle models assume that the residuals of the hurdle equation(s) and the outcome equation are uncorrelated. This will be assessed graphically.

6 SECONDARY OUTCOMES ANALYSIS

6.1 BINARY OUTCOMES

The proportion of patients with each of the serious maternal complications listed in section 3.2.3, the proportion of infants <3rd centile for birthweight and the proportion of women who have completed ≥90% of expected home blood pressure reading (fidelity) will be presented descriptively, with no formal statistical comparison between groups.

All other binary outcomes will be presented and analysed as follows:

TABLE 3: DUMMY TABLE FOR BINARY OUTCOMES

	USUAL CARE	SELF MONITORING	OVERALL
Number (%) of participants with outcome			
	RELATIVE RISK*	95% CI	P-VALUE

*Self-monitoring vs. usual care; estimated from generalised linear mixed effects model with Poisson distribution, log link function and robust standard errors, adjusting for parity and recruitment site

A generalised linear mixed effects model with a Poisson distribution, a log link function, and robust standard errors will be used to analyse the binary outcomes. Randomised group and parity will be included in the model as a fixed effects and site will be included as a random effect if deemed necessary, or fixed effect otherwise. The adjusted relative risk between the intervention arm and the usual care arm with the associated 95% confidence interval and P-value will be derived from the model.

If the model fails to converge we will analyse the outcomes using logistic regression adjusting for site and parity. In this case odds ratios will be presented with 95% confidence intervals and the related P-value.

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 and early neonatal deaths. If less than 2% 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.

6.2 CONTINUOUS OUTCOMES

The following continuous outcomes will be presented descriptively using mean, standard deviation, median, interquartile range and range with no formal statistical comparison between groups:

Birthweight

Centile of birthweight

Mean clinic measured systolic blood pressure

Mean clinic measured diastolic blood pressure

The percentage of expected home blood pressure readings (fidelity)

All other secondary continuous outcomes will be presented and analysed as follows:

TABLE 4: DUMMY TABLE FOR CONTINUOUS OUTCOMES

		USUAL CARE	SELF MONITORING	OVERALL
30 week follow up^	**Mean (SD) Median (IQR) [range]**			
Postnatal follow up	**Mean (SD) Median (IQR) [range]**			
	DIFFERENCE IN MEANS* OR MEDIANS**		**95% CI**	**P-VALUE**
30 weeks^				
Postnatal				

*Self-monitoring vs. usual care; estimated from linear mixed effects model adjusting for parity and recruitment site
^If applicable
**Self-monitoring vs. usual care; estimated from quantile regression adjusting for parity and recruitment site

A linear mixed effect 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 and an interaction term for the treatment by visit interaction to allow the treatment effect to be estimated at each time point. Included in the model will be fixed effects for randomised group and parity and baseline value of the outcome of interest (where applicable). Study site will be included in the model as a random effect if deemed necessary, or fixed effect otherwise. Adjusted mean differences between randomised groups with 95% confidence interval and P value will be estimated from the model at each applicable time point.

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.

Length of stay on the neonatal unit and gestation at delivery are likely to be highly skewed. The groups will therefore be compared using quantile regression, adjusting for parity and site. The difference in medians with 95% confidence interval and associated P-value will be presented. We will also present the mean (SD) in each group.

6.3 CATEGORICAL OUTCOMES (WITH MORE THAN 2 CATEGORIES)

The categorical outcomes (mode of delivery, onset of labour and indication for induction of labour or pre-labour caesarean section) will be summarised descriptively, with the proportion in each category. There will be no statistical analysis comparing randomised groups.

TABLE 5: DUMMY TABLE FOR CATEGORICAL OUTCOMES

	USUAL CARE	SELF MONITORING
	N(%)	N(%)
Mode of delivery		
Spontaneous vaginal delivery		
Assisted vaginal delivery		
Emergency pre-labour caesarean section		
Emergency caesarean section in labour		
Elective pre-labour caesarean section		
Onset of Labour		
Spontaneous		
Induction		
Pre-labour caesarean section		
Pre-labour rupture of membranes/stimulation of labour		
Indication for induction of labour or pre-labour CS*		
Pre-eclampsia		
Chronic hypertension only		
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 prelabour rupture of membranes		
Antepartum haemorrhage		
Fetal growth restriction		
Other		

*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

The adapted beliefs about medicines and adapted brief illness perception questionnaires will be presented graphically using divergent stacked bar graphs. This will be done by randomised group and at each time point (baseline, 30 week follow up and post-natal follow up). There will be no statistical analysis comparing randomised groups.

7 SENSITIVITY ANALYSIS

The trial steering committee proposed a sensitivity analysis where the definition of developing hypertension excludes those who are included only on the basis of being prescribed an antihypertensive. An analysis of the primary outcome will therefore be carried out, defining someone as hypertensive based solely on blood pressure readings. Therefore, if they have no high blood pressure readings but have been prescribed an antihypertensive, they will not be classed as being hypertensive. The analysis will follow the same procedure described in section 5.

8 SUBGROUP ANALYSES

We will carry out sub-group analyses of the primary outcome for the following baseline factors: eligible for aspirin; gestational age at recruitment; parity; measuring BP prior to randomisation; depravation score; ethnicity; qualifications. The analysis population for these analyses will be the same as for the primary analysis. A subgroup effect will be investigated through fitting an interaction term for subgroup x randomised group. The results for all subgroup analyses will be reported in a forest plot, along with the overall treatment effect. In addition to the effect size and 95% CI for the treatment effect in each level of subgroup, the P value for the interaction term will be reported.

1. Eligible for aspirin at baseline

Eligibility for aspirin will be categorised as:

Eligible

Ineligible

A woman is defined as being eligible for aspirin if they have at least one severe risk factor, or at least 2 moderate risk factors for pre-eclampsia. These are listed below, along with their variable name in the dataset (1=yes in all cases):

Severe risk factors:

- Previous history of gestational hypertension of pre-eclampsia (ic4e_bl1)
- Chronic kidney disease (ic4g_bl1)
- Pre-pregnancy diabetes (type I or II) (ic4i_bl1)
- Autoimmune disease (ic4j_bl1)

Moderate risk factors:

- Age 40 years or older (ic4a_bl1)
- Nullparity (first pregnancy) (ic4b_bl1)
- Pregnancy interval of more than 10 years (ic4c_bl1)
- Family history of pre-eclampsia (ic4d_bl1)
- Body mass index of ≥35kg/m^2 at time of booking (this will need to be derived from the BMI variable bmi_bl1)
- Twin pregnancy (ic4h_b1)

2. Gestational age at baseline

Gestational age will be categorised as:

≤20 weeks

>20 weeks

The number of weeks gestation will be calculated as the full number of weeks gestation + (days gestation/7)

The variables to use for this calculation are gestw_bl1 and gestd_bl1.

3. Parity

Parity will be categorised as:

0

≥1

Parity is recorded in the variable ' pari1_bl1' on the baseline CRF.

4. Measuring blood pressure prior to randomisation

Measuring blood pressure during the current pregnancy, prior to randomisation will be categorised as:

Yes

No

This information is recorded in the baseline CRF in the variable 'bpmeas_bl1'.

5. Deprivation score

The index of multiple deprivation will be established from the postcode recorded in the baseline CRF (postco_bl1). Deprivation will be categorised into 2 groups split by the median value.

6. Ethnicity

Ethnicity will be categorised as:

White British or white Irish

Asian/Asian British, black/black British, Chinese, Mixed or other

Ethnicity is recorded in the variable ' ethnic_bl1' on the baseline CRF

7. Qualifications

Qualifications will be categorised as:

Post graduate or above

First degree or professional qualifications

A-level or equivalent, GCSE, O-Level or CSE, vocational qualifications or no formal qualifications

Qualifications are recorded in the variable 'edlevel_bl1' on the baseline CRF.

9 SAFETY ANALYSIS

All women randomised will be included in the safety analysis.

All serious adverse events (SAE) occurring during the trial shall be detailed and reported by treatment group. 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 6: 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
Number of SAEs			
Number of participants experiencing at least one SAE	**N(%)**	**N(%)**	**N(%)**
Difference in proportions, 95% C.I			
Test for difference in proportions (χ^2(df), p-value)			

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

*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

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.

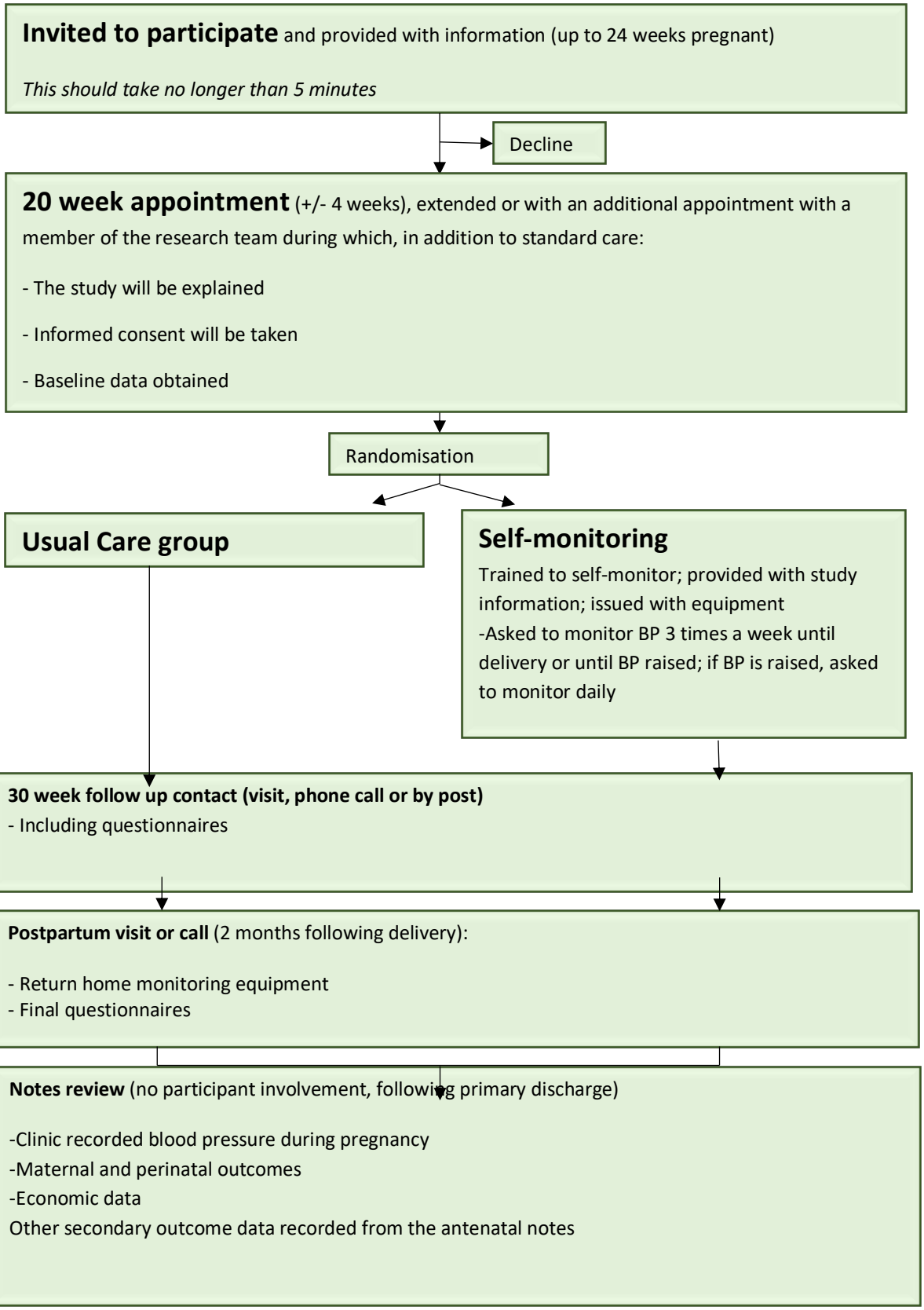
The mean systolic and diastolic clinic measured blood pressures were not stated as outcomes in the protocol. However, they were specified prior to data lock.

The subgroup analyses were not specified in the protocol but were specified prior to data lock.

The protocol states that binary outcomes will be analysed using a logistic mixed effects regression model. However, it was decided to use a Poisson model with robust standard errors so that we could summarize the comparisons using relative risks rather than odds ratios.

12 APPENDICES

Appendix I. Study Flow Chart



Appendix II. Flow diagram of trial participants