

MANAGEMENT OF HYPERTENSIVE DISORDERS OF PREGNANCY IN THE POSTPARTUM PERIOD

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Dedication

To Robert Kennedy – for your unending support, friendship and love.

To Sir Hugh William Bell Cairns – a visionary, surgeon and teacher. Eighty years ago, you saw your neurosurgical outpatients in the building in which this thesis was written. I would like to have known you.

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Abstract

This thesis aimed to explore whether self-management techniques, effective in essential hypertension, could be applied to women with hypertensive disorders of pregnancy postpartum (HDP). HDP affect one in ten pregnancies, remain a leading cause of maternal death worldwide and are associated with elevated long-term maternal cardiovascular risk. Hypertension often persists postpartum and complications can occur. During the puerperium, multiple stresses on new mothers and their healthcare professionals can distract from good quality blood pressure (BP) management. Transfer of responsibility, from secondary to primary care, increases scope for uncertainty. The primary objective was to develop and test the feasibility of a novel self-management intervention for postnatal antihypertensive treatment.

A systematic literature review (39 studies), local audit (n=20) and regional survey (n=101) were conducted to evaluate existing evidence and clinical practice. A pilot randomised controlled trial compared self-management of postnatal antihypertensive medication with usual care (n=91). Taking patients' views of self-management into account is essential to successful implementation and these were captured through qualitative interviews (n=68). A sub-study to assess markers of vascular risk (n=16) was conducted to further evaluate the relationship between postnatal BP and elevated long-term cardiovascular risk.

There is a lack of good quality evidence underpinning hypertension management postpartum and widespread inconsistencies in approaches to care. The pilot trial suggested that expanding the study would be feasible, and that self-management may be more effective than usual care in terms of BP control. Strikingly, the 4-5mmHg reduction in diastolic BP observed with self-management persisted to six months, despite the majority of women being off treatment by this stage, reinforcing the idea that BP control during the puerperium may influence cardiovascular remodelling. However, no differences were demonstrated in markers of cardiovascular risk between sub-study groups.

Participants commonly preferred self-management to usual care, and reported feeling more in control through this approach.

Abbreviations

ABPM		Ambulatory blood pressure monitoring
ACOG		American College of Obstetricians and Gynecologists
Aix		Augmentation index
APTT		Activated partial thromboplastin time
ASH		American Society of Hypertension
BMI		Body mass index
BP		Blood pressure
CAVI		Cardio-ankle vascular index
CI		Chief Investigator
95% CI		95% Confidence interval
CRF		Case report form
CTU		Clinical Trials Unit
CVD		Cardiovascular disease
DBP		Diastolic blood pressure
DMEC		Data Monitoring and Ethics Committee
ESC		European Society of Cardiology
ESH		European Society of Hypertension
GP		General practitioner
HBPM		Home blood pressure monitoring
HDP		Hypertensive disorders of pregnancy
IMD		Index of multiple deprivation
INR		International normalised ratio
IQR		Interquartile range
IRAS		Integrated Research Application System
ISSHP		International Society for the Study of Hypertension in Pregnancy
MAP		Mean arterial pressure
NHS		National Health Service
NICE		National Institute of Health and Care Excellence
NIHR		National Institute for Health Research
OR		Odds ratio
PCR		Protein:creatinine ratio
PIGF		Placental growth factor
PN		Postnatal
PNRA		Postnatal readmission
PRECOG		Pre-eclampsia Community Guidelines
PWV		Pulse wave velocity
PET		Pre-eclampsia
RCT		Randomised controlled trial
REC		Research Ethics Committee
SAE		Serious adverse event
SBP		Systolic blood pressure
SD		Standard deviation
sEng		Soluble endoglin
sFlt1		Soluble FMS-like tyrosine kinase 1
SMS		Short message service
SVR		Systemic vascular resistance
SOGC		Society of Obstetricians and Gynaecologists of Canada
SOMANZ		Society of Obstetric Medicine of Australia and New Zealand
TMG		Trial Management Group
VEGF-1		Vascular endothelial growth factor 1
WHO		World Health Organisation

Table of Contents

Chapter 1: Introduction.....	15
1.1 Overview of the thesis.....	16
1.2 Objectives.....	16
1.3 Definitions	16
1.4 Epidemiology	25
1.5 Physiology of blood pressure in pregnancy and postpartum	26
1.6 Pathophysiology of hypertensive disorders of pregnancy	29
1.7 Hypertensive disorders of pregnancy postpartum	33
1.7.1 Time course.....	33
1.7.2 Complications of postpartum hypertension	36
1.7.3 Management of hypertension postpartum: evidence and guidelines	38
1.8 Hypertensive disorders of pregnancy and long-term cardiovascular risk: epidemiology .	44
1.9 Self-management of blood pressure	46
1.9.1 ‘White coat’ hypertension	46
1.9.2 Self-management of chronic hypertension in the general population.....	46
1.9.3 Self-management of blood pressure in pregnancy.....	47
1.9.4 Telemonitoring.....	50
1.10 Implementation of self-management interventions	51
1.11 Research questions	56
 Chapter 2: Systematic review of the management of hypertensive disorders of pregnancy in the postpartum period.....	 58
2.1 Overview	59
2.2 Objectives.....	59
2.3 Methods	60
2.3.1 Prospective registration and reporting.....	60
2.3.2 Data sources and searches.....	60
2.3.3 Criteria for considering studies for this review.....	60
2.3.4 Study selection.....	61
2.3.5 Data extraction and quality assessment	61
2.3.6 Data synthesis and analysis.....	63
2.4 Results.....	63
2.4.1 Search results.....	63

2.4.2	Characteristics of included studies	63
2.4.3	Summary of main results	76
2.5	Discussion	99
2.5.1	Main Findings	99
2.5.2	Strengths and limitations	100
2.6	Conclusions.....	102
Chapter 3: Local audit and regional survey of postnatal hypertension management ..		104
3.1	Overview	105
3.2	Objectives.....	105
3.3	Audit of postnatal hypertension management	106
3.3.1	Audit: Standards.....	106
3.3.2	Audit: Methods	109
3.3.3	Audit: Results	110
3.4	Postnatal antihypertensive medication adjustment survey.....	113
3.4.1	Survey: Research questions	114
3.4.2	Survey: Methods	114
3.4.3	Survey: Results	115
3.5	Discussion	120
Chapter 4: Self-mANagement of Postnatal antiHypertensive Treatment: the SNAP-HT		
open-label randomised controlled pilot trial		124
4.1	Overview	125
4.2	Objectives.....	125
4.3	Intervention development.....	126
4.3.1	Home blood pressure monitoring.....	127
4.3.2	Blood pressure thresholds	128
4.3.3	Medication adjustment schedules.....	131
4.3.4	Telemonitoring.....	133
4.3.5	Safety	137
4.3.6	System testing.....	139
4.3.7	Participant and staff training	141
4.4	Trial set-up and management	142
4.4.1	Protocol.....	142
4.4.2	Clinical Trials Unit (CTU).....	147
4.4.3	Sponsor	148

4.4.4	Trial Management Group (TMG)	149
4.4.5	Data Monitoring and Ethics Committee (DMEC)	150
4.4.6	Research Ethics Committee (REC) approval.....	151
4.4.7	Research and Development approval.....	152
4.4.8	ClinicalTrials.gov registration	153
4.4.9	NIHR Portfolio adoption.....	154
4.5	Study	155
4.5.1	Objectives.....	155
4.5.2	Methods	155
4.5.3	Results.....	163
4.5.4	Discussion.....	181
4.5.5	Conclusions	185
 Chapter 5: Participant experience of self-management of postnatal antihypertensive treatment: a qualitative sub-study..... 187		
5.1	Objectives.....	188
5.2	Background.....	189
5.2.1	Theoretical approach	190
5.2.2	Qualitative interviews	191
5.2.3	Sampling in qualitative research	192
5.2.4	Analysis	194
5.3	Methods	196
5.4	Results.....	199
5.4.1	Study participants	199
5.4.2	Analysis of audio-recorded, free-text responses	202
5.4.3	Analysis of pre-coded numerical responses	221
5.5	Discussion.....	224
5.5.1	Main findings.....	224
5.5.2	Comparison to the published literature.....	227
5.5.3	Variation in findings according to participant characteristics	229
5.5.4	Strengths and weaknesses.....	229
5.6	Conclusions.....	230
 Chapter 6: Postnatal changes in markers of vascular risk in SNAP-HT participants: a sub-study 232		
6.1	Objectives.....	233

6.2	Background.....	235
6.2.1	Hypertensive disorders of pregnancy and long-term cardiovascular risk: potential mechanisms	235
6.2.2	Vascular dysfunction measures	237
6.2.3	Biomarkers in pre-eclampsia	238
6.3	Methods	239
6.3.1	Sub-study participants	239
6.3.2	Sub-study design	239
6.3.3	Sub-study statistical analysis.....	241
6.4	Results	242
6.4.1	Sub-study participants	242
6.4.2	Arterial stiffness	243
6.4.3	Serum analyses	246
6.5	Discussion	249
6.5.1	Main findings.....	249
6.5.2	Strengths and weaknesses.....	250
Chapter 7:	Conclusions.....	252
7.1	Overview	253
7.2	Epidemiology	253
7.3	Hypertensive disorders of pregnancy postpartum	253
7.4	Existing evidence.....	255
7.5	SNAP-HT pilot randomised trial	256
7.6	By what mechanism(s) might self-management lower blood pressure?	257
7.7	Hypertensive disorders of pregnancy and long-term cardiovascular risk: summary	257
7.8	Implications for practice	258
7.9	Recommendations for research	258
7.10	Final conclusions	259
References		260
Appendices		286

List of Tables

Table 1: Comparison of different definitions of the hypertensive disorders of pregnancy (English language national and international clinical practice guidelines)	19
Table 2: Mapping of end organ complications of pre-eclampsia included in different definitions (English language national and international clinical practice guidelines).....	23
Table 3: Comparison of management of hypertensive disorders of pregnancy postpartum (English language national and international clinical practice guidelines)	41
Table 4: Outcome measures	62
Table 5: Characteristics of included studies (n=39)	66
Table 6: Excluded studies (n=35)	74
Table 7: Risk of bias in included randomised controlled trials and quasi-randomised studies (n=32)	75
Table 8: Risk of bias in included cohort studies (n=7)	76
Table 9: Primary outcome and safety data reporting in included studies (antihypertensive medications, 18 studies)	80
Table 10: Primary outcome and safety data reporting in included studies (loop diuretics, other drugs, uterine curettage and organisation of care, 22 studies)	87
Table 11: Main results (39 studies).....	90
Table 12: Audit participant characteristics (n = 20, including one twin pregnancy)	111
Table 13: Summary of invitations and responses for survey	115
Table 14: Postpartum antihypertensive medication selection	116
Table 15: Commonest postpartum antihypertensive medication.....	116
Table 16: Audit recommendations	121
Table 17: Blood pressure thresholds for self-management (on treatment)	130
Table 18: Blood pressure thresholds for self-management (off treatment)	131
Table 19: Automated SMS responses	135
Table 20: Timing of reminder messages for missed readings.....	138

Table 21: Example of a virtual testing patient	140
Table 22: Baseline characteristics (n=91)	164
Table 23: Recruitment periods	167
Table 24: Recruitment rates at each site	167
Table 25: Potential participants not enrolled (declined versus ineligible)	168
Table 26: SNAP-HT protocol deviations	169
Table 27: Feasibility measures	170
Table 28: Mean follow-up blood pressure readings	173
Table 29: Mean of mean blood pressure readings across follow-up.....	174
Table 30: Proportion of blood pressure readings inside target range at follow-up	175
Table 31: Proportion of blood pressure readings outside safety ranges at follow-up	176
Table 32: Duration of postnatal antihypertensive treatment	176
Table 33: Postnatal readmissions and safety data	177
Table 34: EQ-5D-5L scores	178
Table 35: Analysis of differences between clinic and home blood pressure readings in intervention group.....	180
Table 36: Coding framework.....	198
Table 37: Baseline characteristics of interviewees from self-management group (n=34)	200
Table 38: Baseline characteristics of interviewees from usual care group (n=34)	201
Table 39: Analysis of qualitative patient experience interviews (questions 1-4, both groups).....	223
Table 40: Analysis of qualitative patient experience interviews (questions 6-10, intervention group)	224
Table 41: Baseline characteristics of vascular risk sub-study participants (n=16).....	242
Table 42: Markers of arterial stiffness	245
Table 43: Analysis of serum samples, comparison between study groups	247
Table 44: Analysis of serum samples, comparison between time points.....	248

List of Figures

Figure 1: Serial blood pressures before, during and after pregnancy (reproduced from the data of Mahendru <i>et al.</i> 2014) (32).....	26
Figure 2: Time trend of clinic blood pressure during pregnancy between parity (copied from Ishikuro <i>et al.</i> 2013) (33).....	28
Figure 3: Mean blood pressure by gestational age and parity for white gravidas 25 to 24 years of age who delivered single live term births (copied from Christianson <i>et al.</i> 1976) (34)	29
Figure 4: Opportunities for digital health care to improve productivity and care quality (copied from Nuffield Trust 'Delivery the benefits of digital health care' 2016) (164)	52
Figure 5: Four possible ways that qualitative and quantitative methods might be integrated (copied from Steckler <i>et al.</i> 1992) (178)	54
Figure 6: PRISMA Flowchart.....	65
Figure 7: Antihypertensive medication prescription postpartum	110
Figure 8: Medical follow-up postpartum	112
Figure 9: Details of care plans.....	113
Figure 10: Systolic blood pressure thresholds for medication reduction.....	117
Figure 11: Diastolic blood pressure thresholds for medication reduction	117
Figure 12: Systolic blood pressure thresholds for medication increase	118
Figure 13: Diastolic blood pressure thresholds for medication increase	118
Figure 14: Approach to down-titration.....	119
Figure 15: Approach to down-titration of multiple medications.....	119
Figure 16: Overview of telemonitoring service.....	134
Figure 17: SNAP-HT Study Flowchart	158
Figure 18: Recruitment targets	160
Figure 19: Consort flowchart (enrolment, randomisation, follow-up and analysis)	165
Figure 20: Geographical location of participants by town.....	166

Figure 21: Geographical location of SNAP-HT participants by county.....	166
Figure 22: Adjusted recruitment targets and rates	167
Figure 23: Raw mean systolic and diastolic blood pressures across follow-up	172
Figure 24: Proposed theoretical model illustrating factors influencing implementation & adoption of self-management for postnatal hypertension	226

Chapter 1: Introduction

1.1 Overview of the thesis

Hypertensive disorders of pregnancy (HDP) affect one in ten pregnancies and often persist postpartum. This volume of work examines existing evidence and guidance for managing HDP postpartum, and evaluates the existing practices of clinicians. Following this, a novel self-management intervention for postpartum antihypertensive management is described, which was developed and tested in a randomised pilot study, to answer the over-arching research question: is self-management of hypertension during the postnatal period, in women with new-onset hypertension in pregnancy, feasible, acceptable and effective?

1.2 Objectives

In this introductory chapter, an overview is provided of the definitions and epidemiology of HDP, as well as their pathophysiology. What is known about the postpartum course, complications and management of HDP is examined in detail, before exploring the existing evidence base for self-management of hypertension in the non-pregnant population, and how to approach implementation of health technology in order to achieve successful adoption.

1.3 Definitions

HDP include gestational hypertension, pre-eclampsia, chronic or pre-existing hypertension and superimposed pre-eclampsia. There are multiple different definitions for these conditions in the international literature: from a review of the literature, and contact with experts in this field, ten current English-language clinical practice guidelines were identified that provide definitions for these conditions (Table 1). The following definitions have been agreed by the majority of guidelines: hypertension is defined as a systolic blood pressure (SBP) of ≥ 140 mmHg, and/or a diastolic blood pressure (DBP) of ≥ 90 mmHg. It can either be “chronic”, i.e. pre-existing, or develop during pregnancy. There is some conflict in the guidelines whether new-onset raised blood pressure (BP) in the first half of pregnancy is definitively pre-existing (1, 2). In the absence of proteinuria or other

metabolic abnormality, new-onset hypertension developing in the second half of pregnancy (beyond 20 weeks) is known as gestational hypertension. New-onset hypertension beyond 20 weeks, in the presence of significant proteinuria, plus or minus end organ effects (Table 1 and Table 2), is known as pre-eclampsia. Significant proteinuria is a urinary protein excretion of 300mg or greater in 24 hours. This is translated in some guidelines to be equivalent to a spot urinary protein:creatinine ratio (PCR) of 30mg/mmol (equivalent to 0.26mg/mg, usually rounded to 0.3mg/mg) or higher.

Pre-eclampsia can adversely affect multiple maternal organ systems, including the renal, hepatic and neurological systems (Table 2), and may compromise the developing fetus through placental insufficiency (section 1.6), growth restriction and placental abruption. These effects can result in serious maternal and neonatal morbidity and mortality.

The UK (National Institute for Health and Care Excellence (NICE) and Pre-eclampsia Community Guidelines (PRECOG)), European Society of Cardiology (ESC), American Society of Hypertension (ASH) and World Health Organisation (WHO) guidelines rely solely on the combination of hypertension and proteinuria for their definitions of pre-eclampsia (1, 3-7). However, four other guidelines also include the end organ effects of the condition in their definitions of pre-eclampsia (Table 2) (2, 8-10). The Canadian guideline (2014) includes the most comprehensive list of complications (9), whilst the American College of Obstetricians and Gynecologists' (ACOG) guideline (2013) is most selective (8). A potential pitfall of a very inclusive diagnostic definition is that some signs and symptoms could be attributable to underlying pathology other than pre-eclampsia. All four guidelines include the following five criteria: reduced platelet count (commonly $<100,000/\mu\text{L}$), elevated liver transaminases (at least twice upper limit of normal), right upper quadrant or epigastric pain, elevated serum creatinine ($>90\mu\text{mol/L} \approx >1.1\text{mg/dL}$) and visual disturbances.

Eclampsia is a convulsive condition associated with pre-eclampsia. Women develop generalised tonic-clonic seizures, which are normally self-terminating, without another cause. 'HELLP syndrome' is a severe complication associated with pre-eclampsia – first formally described in 1982 in a case

series of 29 patients – and is defined as haemolysis, elevated liver enzymes and low platelets (11). For several decades prior to this, case reports and small case series were published describing the clinical entity without applying a label (12-14).

Table 1: Comparison of different definitions of the hypertensive disorders of pregnancy (English language national and international clinical practice guidelines)

	PRECOG I (2004) (3) & II (2009) (4)	ASH (2008) (7)	WHO (2011) (6)	ESC (2011) (5)	NICE (2011) (1)	ACOG (2013) (8)	SOGC (2014) (9)	ISSHP (2014) (2)	SOMANZ (2014) (10)
	UK	USA	International	European	UK	USA	Canada	International	Australasia
Hypertension	DBP ≥90mmHg	SBP ≥140mmHg OR DBP ≥90mmHg (two readings 4-6h apart)	DBP >90mmHg	SBP ≥140mmHg OR DBP ≥90mmHg	SBP ≥140mmHg AND/OR DBP ≥90mmHg	SBP ≥140mmHg AND/OR DBP ≥90mmHg (two readings, ≥4h apart)	SBP ≥140mmHg AND/OR DBP ≥90mmHg (average of ≥2 office measurements, ≥15 min apart)	SBP ≥140mmHg AND/OR DBP ≥90mmHg	SBP ≥140mmHg AND/OR DBP ≥90mmHg
Severe hypertension	Not defined	SBP ≥160mmHg AND/OR DBP ≥110mmHg	Not defined	SBP ≥160mmHg AND/OR DBP ≥110mmHg	SBP ≥160mmHg AND/OR DBP ≥110mmHg	SBP ≥160mmHg AND/OR DBP ≥110mmHg	SBP ≥160mmHg AND/OR DBP ≥110mmHg (average ≥2 office measurements, ≥15min apart)	SBP ≥160mmHg AND/OR DBP ≥110mmHg*	SBP ≥170mmHg +/- DBP ≥110mmHg
Significant proteinuria	Spot urinary PCR ≥30mg/mmol OR Urine protein excretion of ≥300mg/24h OR ≥1+ (0.3g/l) on dipstick testing	Spot urinary PCR ≥0.3mg/mg OR Urine protein excretion ≥300mg/24h OR ≥1+ on dipstick testing	Urine protein excretion of ≥300mg/24h	Spot urinary PCR ≥30mg/mmol OR Urine protein excretion of ≥300mg/24h	Spot urinary PCR ≥30mg/mmol OR Urine protein excretion of ≥300mg/24h	Spot urinary PCR ≥0.3mg/mg OR Urine protein excretion of ≥300mg/24h	Spot urinary PCR ≥30mg/mmol OR Urine protein excretion ≥300mg/24h	Spot urinary PCR ≥0.3mg/mg or ≥30mg/mmol OR Urine protein excretion of ≥300mg/24h OR ≥1g/L [2+] on dipstick testing	Spot urinary PCR ≥30mg/mmol
Gestational hypertension	New hypertension ≥20/40 (where DBP <90mmHg <20/40)	New hypertension >20/40	New hypertension during pregnancy, usually during the second half of pregnancy	New hypertension >20/40, usually resolves by 42 days postpartum	New hypertension >20/40, without significant proteinuria	New hypertension >20/40, without significant proteinuria	New hypertension ≥20/40	New hypertension ≥20/40, without any abnormalities that define pre-eclampsia	New hypertension ≥20/40 without maternal or fetal features of pre-eclampsia, BP normalises within 3 months postpartum

Abbreviations: ABPM = ambulatory blood pressure monitoring; BP = blood pressure; DBP = diastolic blood pressure; HBPM = home blood pressure monitoring; PCR = protein:creatinine ratio; SBP = systolic blood pressure

* Derived from the definition of 'less than severe hypertension' being 140–159/90–109 mmHg

	PRECOG I (2004) (3) & II (2009) (4)	ASH (2008) (7)	WHO (2011) (6)	ESC (2011) (5)	NICE (2011) (1)	ACOG (2013) (8)	SOGC (2014) (9)	ISSHP (2014) (2)	SOMANZ (2014) (10)
Pre-eclampsia	New hypertension and significant proteinuria $\geq 20/40$, confirmed if it resolves after delivery	New hypertension and significant proteinuria, usually $>20/40$	New hypertension with significant proteinuria during pregnancy, usually during the second half of pregnancy	New hypertension and significant proteinuria $>20/40$, usually resolves by 42 days postpartum	New hypertension and significant proteinuria $>20/40$	New hypertension with either new significant proteinuria or any 'severe features' [†] $>20/40$	New hypertension with significant proteinuria OR 'adverse condition' [‡] OR 'severe complication' [§] $\geq 20/40$	New hypertension with significant proteinuria OR 'maternal organ dysfunction' ^{**} OR 'uteroplacental dysfunction' ^{††} $>20/40$	New hypertension with significant proteinuria OR 'organ involvement' ^{‡‡} $>20/40$

[†] Severe features (ACOG): Platelet count $<100,000/\mu\text{L}$; liver transaminases double normal level; severe persistent right upper quadrant or epigastric pain unresponsive to medication, not accounted for by alternative diagnosis; serum creatinine concentration $>1.1 \text{ mg/dL}$ or doubled in the absence of other renal disease; pulmonary oedema; new-onset cerebral or visual disturbances

[‡] Adverse conditions (SOGC): Headache/visual symptoms; chest pain/dyspnoea; oxygen saturations $<97\%$; elevated WBC count, INR or APTT; low platelet count; elevated serum creatinine; elevated uric acid; nausea or vomiting; right upper quadrant or epigastric pain; elevated serum transaminases, lactate dehydrogenase or bilirubin; low plasma albumin; non-reassuring fetal heart rate; intrauterine growth restriction; oligohydramnios; absent or reversed umbilical artery end diastolic flow on Doppler velocimetry

[§] Severe complications (SOGC): Eclampsia; PRES; cortical blindness; retinal detachment; Glasgow coma scale <13 ; stroke, transient ischaemic attack or reversible neurological deficit; uncontrolled severe hypertension (12hr despite triple antihypertensive therapy); oxygen saturations $<90\%$, need for $\geq 50\%$ oxygen for $>1\text{hr}$, intubation (other than for caesarean section); pulmonary oedema; positive inotropic support; myocardial ischaemia or infarction; platelets $<50 \times 10^9/\text{L}$; transfusion of any blood product; creatinine $>150\mu\text{M}$; new indication for dialysis; hepatic dysfunction (INR >2 in absence of DIC or warfarin); hepatic haematoma or rupture; abruption with evidence of maternal or fetal compromise; reversed ductus venosus A wave; stillbirth

^{**} Maternal organ dysfunction (ISSHP): renal insufficiency (creatinine $>90 \mu\text{mol/L}$; 1.02 mg/dL ; liver involvement (elevated transaminases – at least twice upper limit of normal $\pm$ right upper quadrant or epigastric pain; neurological complications (eclampsia, altered mental status, blindness, stroke, or more commonly hyperreflexia when accompanied by clonus, severe headaches when accompanied by hyperreflexia, persistent visual scotomata); or haematological complications (thrombocytopenia – platelet count $<150,000/\text{dL}$, DIC, haemolysis)

^{††} Uteroplacental dysfunction (ISSHP): fetal growth restriction

^{‡‡} Organ involvement (SOMANZ): Renal involvement (serum creatinine $>90\mu\text{mol/L}$, oliguria $<80 \text{ mL/4h}$); haematological involvement (platelets $<100,000/\mu\text{L}$; haemolysis: schistocytes or red cell fragments on blood film, raised bilirubin, raised lactate dehydrogenase $>600 \text{ mIU/L}$, decreased haptoglobin; disseminated intravascular coagulation); liver involvement (raised serum transaminases, severe epigastric and/or right upper quadrant pain); neurological involvement (eclampsia; hyperreflexia with sustained clonus; persistent, new headache; persistent visual disturbances (photopsia, scotomata, cortical blindness, posterior reversible encephalopathy syndrome and retinal vasospasm); stroke); pulmonary oedema; fetal growth restriction

	PRECOG I (2004) (3) & II (2009) (4)	ASH (2008) (7)	WHO (2011) (6)	ESC (2011) (5)	NICE (2011) (1)	ACOG (2013) (8)	SOGC (2014) (9)	ISSHP (2014) (2)	SOMANZ (2014) (10)
Severe pre-eclampsia	Not defined	Pre-eclampsia with 'more severe features' ^{§§}	Severe hypertension, heavy proteinuria OR substantial maternal organ dysfunction	Pre-eclampsia with severe signs or symptoms ^{***}	Pre-eclampsia with severe hypertension AND/OR symptoms AND/OR biochemical or haematological impairment	Severe hypertension whilst on bed rest or 'severe features' [†]	Pre-eclampsia with one or more 'severe complications' [§]	Difficulty controlling BP or deteriorating clinical conditions (HELLP, impending eclampsia, worsening low platelet count, or worsening fetal growth restriction)	Cites ISSHP (15)
Super-imposed pre-eclampsia	Development of pre-eclampsia in the context of pre-existing hypertension and/or pre-existing proteinuria	Not explicitly defined	Not defined	Pre-existing hypertension associated with further worsening of BP and protein excretion $\geq 3\text{g}/24\text{h}$ $>20/40$	Not defined	Hypertension or proteinuria $<20/40$ who develop proteinuria or hypertension $>20/40$; OR manifest other signs (as above); OR substantial, sustained increased protein excretion	Development of one of the following $\geq 20/40$ in the context of pre-existing hypertension: resistant hypertension; worsening proteinuria; 'adverse condition(s)' [‡] ; 'severe complication'(s) [§]	Development of one or more of the above features of pre-eclampsia in the context of pre-existing hypertension	Development of one or more of the systemic features of pre-eclampsia $>20/40$ (not fetal growth restriction or worsening hypertension alone) ^{‡‡}
Eclampsia	Not defined	Convulsive condition associated with pre-eclampsia	Generalized tonic-clonic seizures in women with pre-eclampsia, not attributable to other causes	Not defined	Convulsive condition associated with pre-eclampsia	New-onset grand mal seizures in women with pre-eclampsia	Not explicitly defined	Not explicitly defined	Convulsions

^{§§} 'More severe features' (ASH): eclampsia; congestive cardiac failure; pulmonary oedema; gestation $<35/40$; severe hypertension; headache; visual disturbances; abdominal pain; oliguria; platelets $<100,000/\mu\text{l}$; haemolysis (schistocytes, elevated bilirubin, elevated LDH); elevated serum creatinine; elevated AST (aspartate aminotransferase); nephrotic range proteinuria ($>3\text{g}/24\text{h}$); fetal growth restriction, abnormal Doppler velocimetry, abnormal fetal heart rate patterns

^{***} Severe signs and symptoms (ESC): Right upper quadrant pain (hepatic oedema or haemorrhage); headache or visual disturbance (cerebral oedema); occipital lobe blindness; hyperreflexia and clonus; convulsions (cerebral oedema); HELLP syndrome

	PRECOG I (2004) (3) & II (2009) (4)	ASH (2008) (7)	WHO (2011) (6)	ESC (2011) (5)	NICE (2011) (1)	ACOG (2013) (8)	SOGC (2014) (9)	ISSHP (2014) (2)	SOMANZ (2014) (10)
HELLP syndrome	Not defined	Haemolysis, elevated liver enzymes and low platelet count	Haemolysis, elevated liver enzymes and low platelet count	Haemolysis, elevated liver enzymes and low platelet count	Haemolysis, elevated liver enzymes and low platelet count	Haemolysis, elevated liver enzymes, and low platelet count	Haemolysis, elevated liver enzymes, and low platelet count	Haemolysis, elevated liver enzymes, and low platelet count	Haemolysis elevated liver enzymes and low platelets count; with or without other pre-eclamptic features
Chronic or pre-existing hypertension	Hypertension pre-pregnancy or <20/40	Not explicitly defined	Not defined	Hypertension pre-pregnancy or <20/40, usually persists beyond 42 days postpartum	Hypertension present at the booking visit or <20/40; or if taking antihypertensive medication when referred to maternity services	Hypertension pre-pregnancy or <20/40	Hypertension pre-pregnancy or <20/40	Hypertension pre-pregnancy	Hypertension pre-pregnancy or <20/40
White coat hypertension	Not defined	Not defined	Not defined	Not defined	Not defined	Hypertension primarily in the presence of health care providers	BP elevated in the office but consistently normal outside of the office: <135/85mmHg by ABPM or HBPM	Elevated clinic or office BP with normal BP by 24h ABPM in the first half of pregnancy	Elevated BP in the presence of a clinical attendant but normal BP otherwise as assessed by ABPM or HBPM

Table 2: Mapping of end organ complications of pre-eclampsia included in different definitions (English language national and international clinical practice guidelines)

	ACOG (2013) (8)	SOGC (2014) (9)	ISSHP (2014) (2)	SOMANZ (2015) (10)
	USA	Canada	International	Australasia
Cardiovascular				
Myocardial ischaemia or infarction		•		
Positive inotropic support		•		
Uncontrolled severe hypertension >12h despite triple antihypertensive therapy		•		
Haematological				
Thrombocytopenia	•	•	•	•
Haemolysis		•	•	•
Disseminated intravascular coagulation			•	•
Elevated white blood cell count, INR or APTT		•		
Transfusion of any blood product		•		
Hepatic				
Elevated transaminases	•	•	•	•
Low plasma albumin		•		
Right upper quadrant / epigastric pain	•	•	•	•
Hepatic haematoma or rupture		•		
Neurological				
Eclampsia		•	•	•
Posterior reversible encephalopathy syndrome		•		•
Cortical blindness		•	•	•
Retinal detachment		•		
Altered mental state		•	•	
Stroke		•	•	
Transient ischaemic attack or reversible neurological deficit		•		
Visual disturbances	•	•	•	•
Headache		•	•	•
Hyperreflexia and/or clonus			•	•
Renal				
Elevated serum or plasma creatinine	•	•	•	•
Elevated uric acid		•		
Oliguria				•

	ACOG (2013) (8)	SOGC (2014) (9)	ISSHP (2014) (2)	SOMANZ (2015) (10)
New indication for dialysis		•		
Respiratory				
Pulmonary oedema	•	•		•
Hypoxia		•		
Need for intubation (other than for caesarean section)		•		
Uteroplacental				
Fetal growth restriction		•	•	•
Oligohydramnios		•		
Absent or reversed umbilical artery end diastolic flow on Doppler velocimetry		•		
Reversed ductus venosus A wave		•		
Non-reassuring fetal heart rate		•		
Placental abruption with evidence of maternal or fetal compromise		•		
Stillbirth		•		
Other				
Nausea and vomiting		•		

1.4 Epidemiology

Until recently, HDP have been the second commonest direct cause of maternal death in both the UK (CMACE 2006-8) (16) and USA (17). Over the course of the last three published UK confidential enquiries into maternal deaths, HDP have fallen to the fourth (18), the fifth (19) and most recently the eighth (20) commonest direct cause of maternal deaths. From 2012-14 the rate of death from HDP was 0.11 per 100,000 maternities (20), a more than seven-fold reduction from the rate of 0.83 per 100,000 for the triennium 2006-8. It is perhaps relevant that in the 2006-8 report the most common cause of substandard care of women with pre-eclampsia, who died, was failure to treat sustained severe hypertension, resulting in the key recommendation that, 'systolic hypertension requires treatment' (16). However, it is unclear to what extent the recognition of the risks associated with severe systolic hypertension has directly influenced the maternal mortality rate.

A recent population-based retrospective study using data from the National Hospital Discharge Survey (120 million births) in the USA found the rate of pre-eclampsia to be 3.4%. This study showed a slight, but significant increase, in the rates of both mild, and to a greater extent, severe pre-eclampsia over the period studied (1980-2010) (21). Reviews of the literature, and national guidelines, quote rates of gestational hypertension between 6% (22) and 15% (23). A retrospective study using data from the National Hospital Discharge Survey in the United States (1987-2004) demonstrated an incidence of 30.6 cases of gestational hypertension per 1000 deliveries in 2003-2004 (3.1%) (24). In a well-designed large randomised controlled trial (RCT) assessing preventative strategies for HDP in low risk, nulliparous women the incidence of gestational hypertension across both groups was 6% (25). With chronic hypertension thought to affect approximately 1% of pregnant women (26) it is therefore reasonable to quote a summary figure that HDP affect approximately one in ten pregnancies, comprising 6% gestational hypertension, 3% pre-eclampsia and 1% chronic hypertension.

Eclampsia only affects a small proportion of hypertensive pregnancies in the developed world. Nationwide data from all maternity units in the Netherlands over a two-year period (2004-2006) produced an incidence of 6.2/10,000 births (27). Similar data from the UK, from the UK Obstetric Surveillance System over a one-year period, gave an incidence of 2.7/10,000 births (28), a substantial reduction from the previously reported rate of 4.9/10,000 maternities (UK data from 1992) (29). A 12-month regional UK case-control study reported an incidence of HELLP syndrome of 0.5/1000 births (30).

In the UK, recent population-level data suggest a trend towards an increased risk of maternal mortality and severe morbidity amongst women from more deprived backgrounds (20, 31), however the observed differences did not reach statistical significance. Nonetheless, it is imperative that any intervention be designed such that it is suitable for use across the population.

1.5 Physiology of blood pressure in pregnancy and postpartum

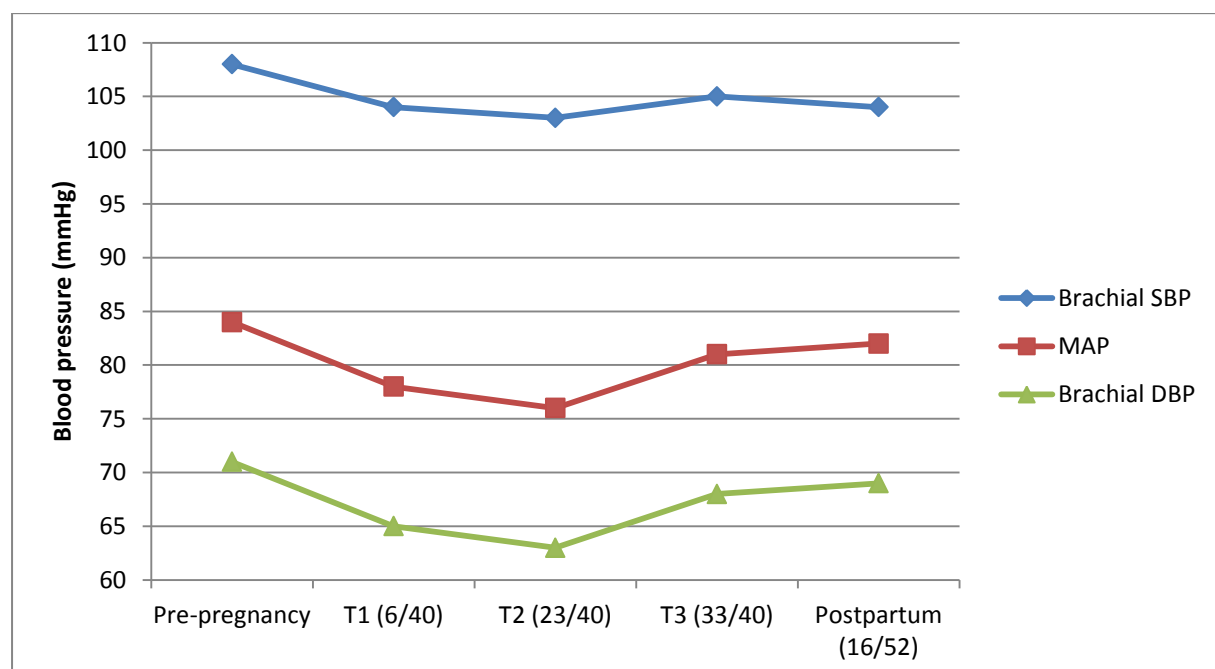


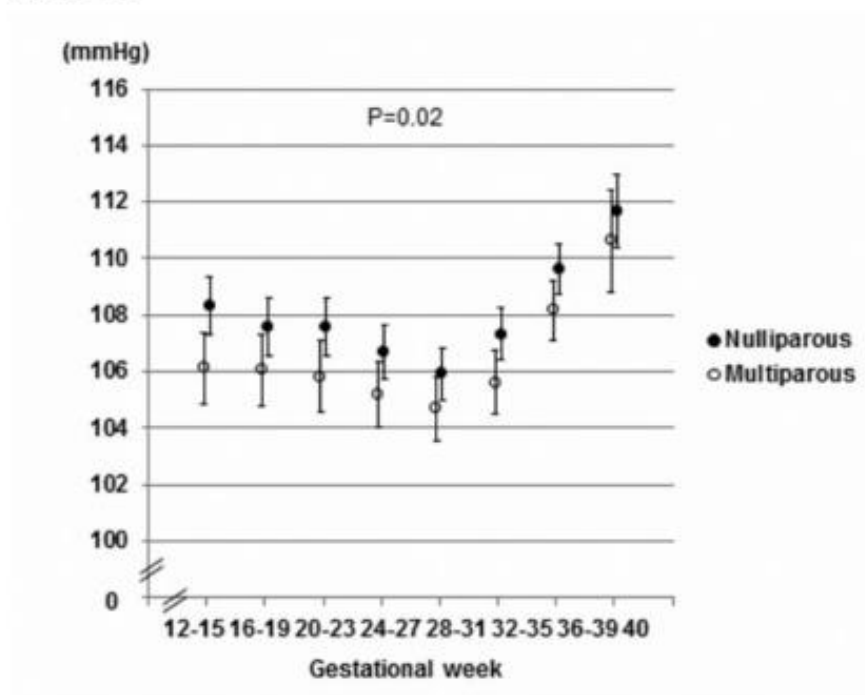
Figure 1: Serial blood pressures before, during and after pregnancy (reproduced from the data of Mahendru *et al.* 2014) (32)

Resulting from a significant decrease in systemic vascular resistance (SVR), seen as early as five weeks of gestation (32), there is a decrease in arterial pressures from early in the first trimester. Arterial pressures reach a nadir in the second trimester, and then begin to rise in the third trimester, before reaching near-preconception levels in the postnatal period.

Two recent prospective observational studies in healthy women with normal pregnancies found similar magnitudes of BP shifts (Figure 1 (n=54) and Figure 2 (n=530)) (33) (34) to those found by an older retrospective study (n=6,662), in women who delivered live singleton, term infants and commenced antenatal care before 20 weeks gestation (Figure 3) (35). The mean BP measurements reported in the retrospective study are substantially higher (10-15mmHg), likely resulting from their unselected population. Unlike the prospective studies, hypertensive women were not excluded.

One prospective study (34) and the retrospective study (35) also demonstrated a difference in mean SBP and DBP between the first and subsequent pregnancies – higher in the first pregnancy – that could reflect a higher incidence of white coat hypertension (section 1.9.1) among first time mothers, who may be unaccustomed to regular BP measurement. This hypothesis is supported by the fact that the prospective study found a difference between nulliparous and multiparous women with clinic BP monitoring (Figure 2), but not with home BP monitoring (HBPM) (34).

a. SBP



b. DBP

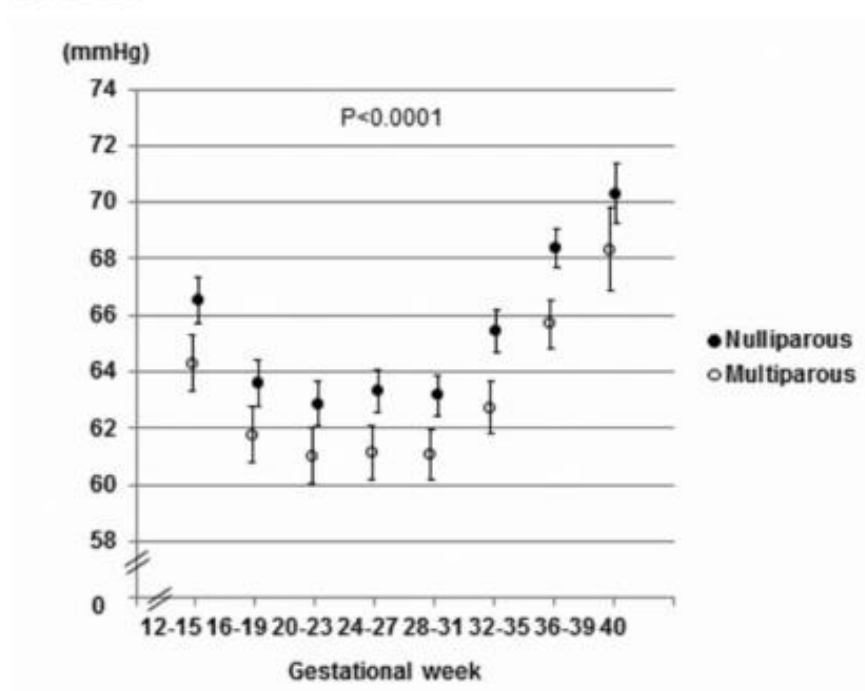


Figure 2: Time trend of clinic blood pressure during pregnancy between parity (copied from Ishikuro *et al.* 2013) (33)

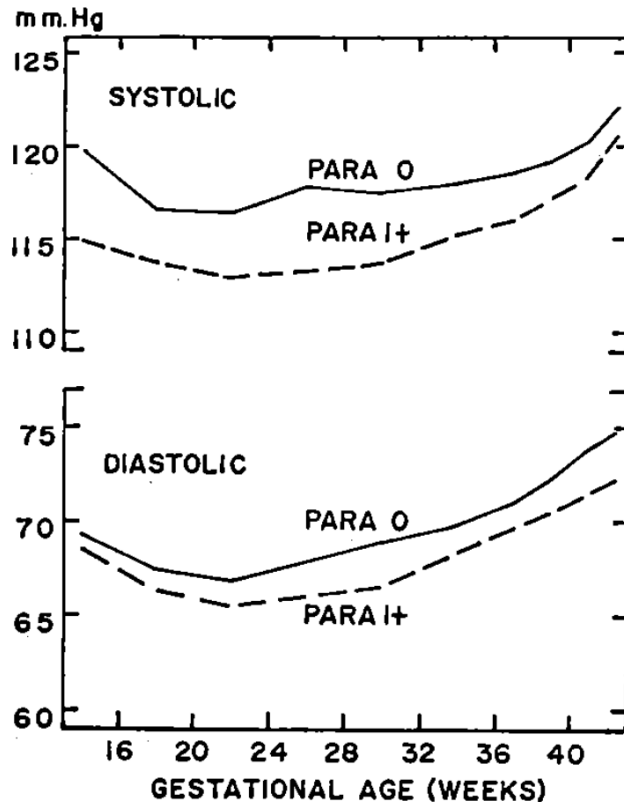


Figure 3: Mean blood pressure by gestational age and parity for white gravidas 25 to 24 years of age who delivered single live term births (copied from Christianson *et al.* 1976) (34)

1.6 Pathophysiology of hypertensive disorders of pregnancy

This section focuses on the suspected cause of pre-eclampsia. Gestational hypertension and pre-eclampsia are believed to be on a spectrum, and therefore the pathophysiology of the two clinically distinct conditions is considered collectively.

It has been known, for almost 80 years, that pre-eclampsia only occurs when there is a placenta present (a fetus is not required as pre-eclampsia can occur with molar pregnancies), and recovers following delivery or removal of the placenta. Ernest Page hypothesised in 1939 that the origin of pre-eclampsia may be placental, describing a significantly higher incidence of pre-eclampsia in a cohort of women with hydatitiform molar pregnancies in the second trimester (77%) than that seen in a cohort of normal pregnancies from the same population (9%). In this manuscript he describes the placenta as a 'ruthless parasitic organ existing solely for the maintenance and protection of the fetus, perhaps too often to the disregard of the maternal organism' (35).

However, beyond its clearly described placental origins, confusion surrounds the exact pathophysiology underlying pre-eclampsia. Multiple mechanisms have been proposed, including immunological and genetic hypotheses. A detailed exploration of the different theories and the controversies in this field are outside the remit of this thesis, however a brief overview of the main hypotheses is presented here.

In gestational hypertension and pre-eclampsia, the normal pregnancy-induced vasodilatation (section 1.5) is believed to be reversed. In untreated women with pre-eclampsia, significant increases in SVR are seen and result in elevation of BP (36). It has been postulated that increased SVR, not increased cardiac output, is the central cause of elevated BP in pre-eclampsia. The vasoconstriction appears to be mediated, in part, by alterations in the concentrations of several vasoactive substances, including noradrenaline, endothelin and perhaps thromboxane (37). Synthesis of the potent vasodilator endothelium-derived nitric oxide appears to be reduced (38). The renin-angiotensin system, which primarily regulates body-fluid volume, is believed to have a pivotal role in pre-eclampsia pathogenesis (39). Evidence exists that in pre-eclampsia there is also an exaggerated response to both endogenous and exogenous vasopressors (37). Perfusion of virtually all organs is compromised, in part due to the vasospasm already described. Perfusion impairment is further influenced by the loss of fluid from the intravascular space seen in pre-eclampsia, and by activation of the coagulation cascade, with resultant microthrombi formation (40).

The mechanism of abnormal placentation, implicated in the development of pre-eclampsia, was first proposed in 1970: impaired invasion of the spiral arteries by the proliferating cytotrophoblast was described (41). In normal pregnancy, mononuclear cytotrophoblasts migrate up the lumina of spiral arterioles, within the wall of the pregnant uterus, and ultimately replace the endothelial lining and part of the muscular wall of these vessels as they traverse the decidua and inner third of the myometrium (42). This vessel remodelling results in an enlarged luminal diameter, and blood vessel walls with a low proportion of smooth muscle, creating a large-bore, high-capacity, low-resistance

uterine circulation for placental perfusion (40). In pre-eclampsia, these modifications fail to take place normally: invasion of the spiral arteries is incomplete, with a reduced number of endovascular cytotrophoblasts. The endothelial lining is retained in places, and the muscular coat remains relatively intact. Therefore the vessels do not enlarge sufficiently to deliver an adequate maternal blood supply to the placenta. Animal models of reduced placental perfusion reproduce clinical features of pre-eclampsia (43).

Placentation occurs early in pregnancy, and is largely complete by twenty weeks gestation, yet the syndrome of pre-eclampsia is rarely seen before mid-gestation. As such, a two-stage progression has been proposed. Over the course of the second two trimesters, the placental demands on the maternal blood supply increase, due to the expanding intervillous space. If the capacity of the spiral arteries is inadequate, they fail to accommodate these demands resulting in placental hypoxia (44). Poor placentation, in the first trimester, is followed, by development of the maternal (and fetal) signs of the condition, caused by an increasingly hypoxic placenta.

The question remains, why does deficient placentation occur? One indication of why this has proved so difficult to answer conclusively is the diverse range of risk factors for developing pre-eclampsia. Women may be at increased risk due to conventional risk factors for cardiovascular disease (CVD), including obesity, advanced age, pre-existing hypertension, ethnicity, diabetes and increased insulin resistance. Intriguingly, however, smoking is protective (45). Cases where there is increased placental mass, including multiple pregnancy and molar pregnancy, also demonstrate increased risk: it is hypothesized that excessive placental size results in relative placental hypoperfusion (46). Primiparity (47, 48), change of partner (primi-paternity) (49), oocyte donation, artificial insemination (50) and intracytoplasmic sperm injection (51) all confer an increased risk. Longer duration of sexual activity with a partner antedating the index pregnancy reduces the risk of pre-eclampsia (52, 53). These observations lead to the 'immune theory' of pre-eclampsia, which proposes that prior

exposure to paternal antigens is protective, and that abnormal placentation is secondary to immune maladaptation.

Pre-eclampsia is not conventionally considered a genetic condition, and does not demonstrate classic Mendelian genetics. However, it has been clear for centuries that some individuals show a strong familial predisposition to developing pre-eclampsia (54, 55). Having a first degree female relative with a history of pre-eclampsia confers a four-fold increased risk of developing severe pre-eclampsia as a primigravida (56). Despite this, numerous genetic studies, both candidate gene and gene-expression, have failed to define a precise genetic basis for the disorder. One potential explanation for the difficulty is the notion that the single clinical phenotype of 'pre-eclampsia' should be separated into different sub-groups on either a genetic or a biochemical basis (57).

Placental ischaemia in isolation, is not all that is required to produce the phenotype of pre-eclampsia (58). As such, it is recognised that the maternal response to ischaemia, either placental or systemic, must vary (37). Oxidative stress has been suggested as the 'missing link' between impaired placental perfusion and the pre-eclampsia phenotype (59). In susceptible women, the poorly perfused placenta may result in generation of reactive oxygen species. Markers of oxidative stress have been identified in the blood of pre-eclamptic patients for several decades (40). This hypothesis generated a potential therapeutic target: use of antioxidants. Small, early clinical trials suggested potential benefit from administration of vitamins C and E in terms of risk reduction (60). However, larger RCTs and systematic reviews of the literature have not confirmed this initial finding (61, 62).

A protracted search has been conducted for the 'placental factor' in the maternal circulation, which serves as the link between abnormal placentation, placental ischaemia and the maternal syndrome. Multiple candidates have been proposed, including tumour necrosis factor- α (63), interleukin-6 (63, 64), interleukin-1 α , interleukin-1 β (64), Fas ligand (65), neurokinin B (66) and asymmetric dimethyl L-arginine (67) but none has been demonstrated to be etiologic (37).

Currently one of the strongest candidates appears to be soluble FMS-like tyrosine kinase 1 (sFlt-1), which is the soluble receptor for vascular endothelial growth factor 1 (VEGF-1) (68, 69). Angiogenesis is the development of new vessels from pre-existing vessels, and is promoted by angiogenic factors such as placental growth factor (PlGF) and VEGF-1 (70). sFlt-1 binds VEGF-1 and also placental growth factor (PlGF), reducing the supply of these essential survival factors to the systemic endothelium, and is therefore antiangiogenic (44). In pre-eclampsia, serum levels of sFlt-1 are increased (first reported in 2003) (71), and levels of PlGF are correspondingly decreased (71, 72). An elevated sFlt-1:PlGF ratio is associated with an increased risk of pre-eclampsia (73), and has been suggested as an adjunctive diagnostic test for pre-eclampsia (74), as the circulating levels change in advance of any clinical manifestation (72, 75). A recent observational study has developed a validated a sFlt-1:PlGF ratio predictive cut-off for use in pre-eclampsia diagnosis (76).

1.7 Hypertensive disorders of pregnancy postpartum

1.7.1 Time course

There has been considerable focus on BP control during pregnancy, especially with respect to pregnancy outcome, and relatively less emphasis on the postnatal period. However, HDP, and complications thereof, frequently persist postpartum. The UK's Chief Medical Officer, dedicated a chapter of her 2014 annual report (The Health of the 51%: Women) to postpartum care, and specifically referred to HDP as an area where there is a lack of evidence based guidance, recommending urgent research into appropriate interventions for inclusion in a comprehensive postnatal package of care (77).

Hypertension can persist postpartum following a pregnancy complicated by hypertension, or can arise for the first time postpartum (within 6 weeks) (78). The mean duration of postpartum hypertension remains unclear from the published literature. It is evident that over a relatively short time period (weeks to months) most women are likely to transition from being significantly

hypertensive, taking potentially relatively large doses of medication, to normal. However, this period can be unpredictable. The rapidly changing BP, with shifting medication requirement, poses a challenge to physicians in terms of how best to manage down-titration of antihypertensive medications and for a woman with a new born baby to look after. American guidelines state that hypertension ought to have resolved by three months postpartum, otherwise this is suggestive of chronic hypertension (17), recommending that if abnormalities persist at the six-week postpartum check, women should be examined six weeks later and investigated for chronic hypertension if they remain hypertensive (79). The NICE guidance is more conservative: recommending referral to a hypertension specialist if treatment for hypertension is ongoing at the six-week postnatal check (1).

A small retrospective observational study looked at 67 women with moderate-severe pre-eclampsia: this showed that although there was often an initial decrease in BP after delivery this was followed by a rise to hypertensive levels in many women. In 50% of cases the BP was $\geq 150/100$ mmHg on day five after birth. The authors recommended continuing BP monitoring and treatment in the postpartum period for women with a diagnosis of pre-eclampsia (80).

There are conflicting reports from the literature regarding average duration of raised BP postpartum in women who develop de novo hypertension in pregnancy. One report suggested that only 31% of women with pre-eclampsia, and 19% with gestational hypertension remained hypertensive on day 7 postpartum. However, the follow-up duration for this study was limited to 7 days, and it is unclear whether these patients remained on antihypertensive medication - i.e. they had BP controlled to $<140/90$ mmHg with treatment (81). An older study ($n=269$) found that the time to BP normalisation was zero to 10 days in gestational hypertension, and zero to 23 days in pre-eclampsia (82). However, they defined a normal BP as a DBP of ≤ 110 mmHg, and antihypertensive medications were reduced or stopped once this threshold was achieved, contrary to current recommendations (1).

Furthermore, women who remained hypertensive beyond day 50 postpartum were excluded. These factors are likely to have artificially shortened the reported duration of postpartum hypertension.

An observational prospective cohort study (n=205) found that 54% of pre-eclamptic women remained hypertensive at six weeks, 39% at three months and 18% at two years (83). However, complete data was only available for 116/205 (57%): this could have introduced bias, as women with ongoing BP problems might have been more likely to attend follow-up, when compared to those who's BP had normalised. In a further retrospective cohort study (n=62), in women whose BP normalised after delivery (women whose BP remained elevated were excluded), the mean time to normalisation was 5.4 weeks (84).

Reports have been conflicting regarding factors that may influence the speed of resolution of HDP postpartum: some studies demonstrate no correlation between disease severity (85) or gestation at onset (83) and time to normalisation. Correlation has been found in some studies between diagnosis (81, 82), maximal SBP (83), maximal proteinuria (83) and time to resolution. Therefore, it seems reasonable to suggest that, at present, the tools, to predict how rapidly an individual's BP will normalise, do not exist.

During the follow-up of a large-scale RCT (HYPITAT) evaluating early induction versus expectant management for mild HDP (86) a subset of women (n=187) had their BP measured postpartum. 40% were found to be hypertensive at six weeks (defined as DBP >90mmHg and/or SBP >140mmHg, or ongoing antihypertensive treatment). Hypertension at six weeks correlated with an increased risk of essential hypertension 2.5 years postpartum: 61% versus 32% in those who were normotensive at six weeks (OR 3.3, 95% confidence interval 1.8 to 6.2) (87).

The majority of evidence available suggests the need for follow-up of BP beyond either the period spent in hospital after birth (typically up to five days for patients with pre-eclampsia), or the final community midwife review (day 10 postpartum). Given the likely need for medication adjustment during this period, and the current lack of ability to accurately predict the speed of resolution, it is also reasonable to propose that simply checking BP at the routine GP check at six-weeks postpartum, which in some cases might be omitted, is unlikely to be adequate. Furthermore, a multi-

centre audit suggested that not all women with pregnancies complicated by pre-eclampsia were having their BP measured (93%) or urine checked for proteinuria (28%) at this follow-up appointment (88). Given the paucity of evidence identified by the NICE guideline development group regarding frequency or timing of observations and monitoring in the postpartum period (section 1.7.3) there is a need to develop strategies to assist both patients and clinicians with management in this period.

1.7.2 Complications of postpartum hypertension

The complications, that may affect women with pre-eclampsia antepartum, can also occur during the postnatal period (section 1.3). Severe hypertension, which may be encountered in gestational hypertension, can result in cerebral haemorrhage or ischaemic stroke, even in the absence of the associated end-organ effects that characterise pre-eclampsia.

A Cochrane review has highlighted little evidence underpinning BP management postpartum, despite recognition that complications of HDP can occur following delivery (89). Approximately 30% of eclampsia occurs after birth, and 14-50% of these seizures happen beyond 48 hours (90-92). An observational study evaluating a year's data from all 229 UK consultant-led units (February 2005 to February 2006) reported an incidence of postpartum eclampsia of 1/10,000 maternities (91). A retrospective cohort study from the USA looked at readmissions postpartum with pre-eclampsia and eclampsia: 152 women (n=48,498 deliveries), over a 6.5-year period, were readmitted with pre-eclampsia (0.3%). In total 22 of these women (0.05%) had eclampsia: six had seizures at home, and five had seizures in the emergency department (0.02%) (93). These numbers are small, but the risks associated with a woman suffering an unexpected seizure, unattended at home with a new baby are significant. The observed incidence of postpartum seizures is supported by physiological studies suggesting that increases in cerebral perfusion pressure seen in pre-eclampsia are maintained for up to one week postpartum (94).

A consecutive case series (n=28) showed that 57% of strokes, sustained in association with severe pre-eclampsia, occurred postpartum (95). This study also correlated preceding severe systolic hypertension (155-160 mmHg), but not severe diastolic hypertension, with strokes in all the women studied (95). The authors suggested a shift in treatment focus towards severe systolic hypertension, and this was subsequently reflected in recommendations from the 2006-8 UK triennial maternal mortality report (16). An American cohort study (n=2,066,230) demonstrated a post-discharge postpartum acute cerebrovascular event rate of 14.8/100,000 (96). This is similar to previously published rates of all postpartum acute cerebrovascular disease (8-22/100,000 deliveries) (97, 98), suggesting a significant proportion of acute events occurs after discharge from hospital. Approximately 20% of the women in this cohort who suffered a post-discharge acute event had a diagnosis of pre-eclampsia or hypertension (96).

Women present to the emergency department not infrequently during the puerperium with BP issues. An American population study (n=222,084) showed that 418 women presented to the emergency department with hypertension or pre-eclampsia-related problems within 100 days of birth. Five women (<0.1%) presented with eclampsia (99). A similar study (n=222,751) evaluated readmissions to hospital within six weeks from their original delivery discharge date: 427 women (0.2%) were readmitted with problems related to hypertension (100). This suggests that the rare, serious morbidity related to pre-eclampsia constitutes a minority of the burden this condition places upon patients and the healthcare system in the postnatal period. Presentations to the emergency department are common, and hospital readmissions related to hypertension occur in 0.2% of the entire postpartum population. If 10% of women have a diagnosis of hypertension in pregnancy (section 1.4), this suggests approximately 2% of the hypertensive population are likely to be readmitted postpartum. As such, models of care, following delivery in a hypertensive pregnancy need to encompass safe care for women at risk of such complications.

1.7.3 Management of hypertension postpartum: evidence and guidelines

International guidelines and a Cochrane review highlight that very few clinical studies have addressed the management of BP postpartum (1, 89). Nine trials were included in the Cochrane review but all concerned the type of medication used postpartum and not models of care (89). NICE concluded that there was no good evidence to determine whether routine postnatal antihypertensive treatment was beneficial in women with HDP, or to advise which drug(s) ought to be used (1).

A systematic review of international clinical practice guidelines was published in 2014 (101). From this, together with an up to date online search, six current English-language national and international clinical practice guidelines were identified, which make some recommendations about postpartum management of HDP (Table 3). From this summary, it seems that the NICE guideline provides the most comprehensive postnatal recommendations (1).

Guidelines from the UK, Canada and the USA all provide some information about BP monitoring after birth (1, 8, 9). NICE recommend a frequency of monitoring in the postnatal period for both pre-eclampsia (at least alternate days to day 14), and gestational hypertension (daily for the first two days, and then at least once between day three to five) (1). As a minimum, NICE recommend a medical review at two and six weeks postpartum. However, they acknowledge that no evidence exists to support the frequency or timing of observations and monitoring (1). Recommendations from ACOG (2013) suggest that BP be monitored in hospital (or with an equivalent level of outpatient surveillance) for 72 hours after birth, and checked again between seven and ten days after birth (or sooner if a woman is symptomatic) (8). Guidance from the Society of Obstetricians and Gynaecologists of Canada (SOGC) only states that BP should be monitored between days three and six postpartum, as it is during this time that BP normally peaks (9).

NICE stipulates expert-derived thresholds for considering increasing or starting ($\geq 150/100$ mmHg), and reducing or stopping (consider reducing $< 140/90$ mmHg, reduce $< 130/80$ mmHg)

antihypertensive medication during this period (1). However, little detail is provided concerning for example dose reduction (frequency and amount), or the approach to management of multiple medications (1). ACOG acknowledges the uncertainty that exists regarding what BP level to treat and when to reduce or stop treatment. In line with NICE, these guidelines propose treating a BP ≥ 150 mmHg systolic or ≥ 100 mmHg diastolic, but add this should be on two repeated measures, four to six hours apart. No suggestion is made about BP thresholds for medication reduction (8). The WHO recommends treatment of severe hypertension postpartum, but do not define BP thresholds (6). The SOGC guideline suggests maintaining BP $< 140/90$ mmHg ($< 130/80$ mmHg if a woman has pre-gestational diabetes mellitus) (9). Neither the European nor Australasian guidelines specify BP thresholds for medication adjustment (5, 10).

Neither ACOG nor the WHO make specific recommendations about antihypertensive selection postpartum (6, 8). The remaining four guidelines recommend a selection of antihypertensive medications, which may be used postpartum, but none commit to which agent should be used preferentially (Table 3). Both NICE and the European Society of Cardiology (ESC) guidelines recommend that methyldopa should be avoided during the postnatal period due to an increased risk of postnatal depression (1, 5). NICE recommend switching it for an alternative antihypertensive within 48 hours of birth (1). Interestingly the UK Medicines and Healthcare products Regulatory Agency state that methyldopa is the antihypertensive agent of choice for use in pregnancy and breastfeeding (102). However, this overlooks the increased risk of depression during the postnatal period, and the known association between methyldopa and depression in the general population (103). The guidelines do not make consistent recommendations about other therapy postpartum: varied statements are made about the avoidance of non-steroidal anti-inflammatory drugs, consideration of thromboprophylaxis and the use of magnesium sulphate in symptomatic or severe hypertension (Table 3).

A message that emerges from the majority from the guidelines is that of the increased long-term cardiovascular risk associated with HDP (section 1.8), and the recommendation for future monitoring of cardiovascular risk measures and lifestyle changes to ameliorate these risks. Three guidelines (UK, Canadian and Australasian) recommend investigation for women with persistent postpartum hypertension and/or proteinuria (1, 9, 10).

Table 3: Comparison of management of hypertensive disorders of pregnancy postpartum (English language national and international clinical practice guidelines)

	WHO (2011) (6)	ESC (2011) (5)	NICE (2011) (1)	ACOG (2013) (8)	SOGC (2014) (9)	SOMANZ (2015) (10)
	International	European	UK	USA	Canada	Australasia
Monitoring						
Hospital discharge criteria	Not specified	Not specified	Asymptomatic; BP <150/100mmHg; blood tests stable or improving	Not specified	Not specified	Not specified
BP monitoring (gestational hypertension)	Maximum increase in BP usually occurs towards the end of the first postpartum week; no comment about monitoring frequency / type	BP usually rises after delivery over the first 5 days; no comment about monitoring frequency / type	Daily for first 2 days, then once day 3-5; medical review at 2 and 6 weeks postpartum	Monitor BP in hospital for 72h; check again between 7-10 days after birth	Measure BP days 3-6 after delivery	Not specified
BP monitoring (pre-eclampsia)	Maximum increase in BP usually occurs towards the end of the first postpartum week; no comment about monitoring frequency / type	BP usually rises after delivery over the first 5 days; no comment about monitoring frequency / type	At least alternate days to day 14; medical review at 2 and 6 weeks postpartum			
Symptom monitoring	Not specified	Not specified	Ask about severe headache and epigastric pain each time BP measured	Not specified	Not specified	Not specified
Other monitoring	Not specified	Not specified	If abnormal, repeat platelet count, transaminases, serum creatinine measurements and urinalysis for proteinuria as clinically indicated and at 6-8 weeks postpartum	Not specified	Confirm end organ dysfunction has resolved	Confirm proteinuria has resolved
BP thresholds						
Up-titration / starting treatment	Recommends treating 'severe hypertension' (not defined)	Not specified	SBP ≥150mmHg AND/OR DBP ≥100mmHg	SBP ≥150mmHg AND/OR DBP ≥100mmHg	Aim to keep BP <140/90mmHg (<130/80mmHg in women with pre-gestational diabetes)	Not specified
Down-titration / stopping treatment	Not specified	Not specified	SBP <130mmHg AND DBP <80mmHg	Not specified		Not specified
Antihypertensive medication						
Recommended	Continue antenatal therapy; no specific recommendations	Continue antenatal therapy	Labetalol Nifedipine Enalapril Captopril Atenolol Metoprolol	Not specified	Nifedipine XL Labetalol Methyldopa Captopril Enalapril	Slow-withdrawal recommended All agents* used antepartum plus enalapril, captopril and quinapril can be used postpartum

* Methyldopa, labetalol, oxprenolol, nifedipine, prazosin, hydralazine, diazoxide

	WHO (2011) (6)	ESC (2011) (5)	NICE (2011) (1)	ACOG (2013) (8)	SOGC (2014) (9)	SOMANZ (2015) (10)
Insufficient evidence / uncertain	Not specified	Propranolol and nifedipine present in similar concentrations in breastmilk to maternal plasma	Amlodipine Other ACE-inhibitors Angiotensin receptor blockers	Not specified	Caution may be exercised in preterm and low birth weight infants	Clonidine accumulates significantly in the neonatal serum (significance uncertain)
Avoid	Not specified	Methyldopa	Methyldopa	Not specified	Not specified	Not specified
Other therapies						
Medications	Not specified	Not specified	Avoid diuretics when breastfeeding	If new-onset postpartum hypertension with headaches/blurred vision or preeclampsia with severe hypertension treat with parenteral magnesium sulphate	Avoid non-steroidal anti-inflammatory drugs if hypertension is resistant or there is evidence of kidney injury (creatinine >90µmol/L) or severe thrombocytopenia (<50x10 ⁹ /L) Consider thromboprophylaxis	Non-steroidal anti-inflammatory drugs are contraindicated
Other interventions	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
Other recommendations						
Information provision	Need for discharge instructions, including education concerning signs and symptoms associated with postpartum hypertension.	Not specified	Write care plan detailing who will provide follow-up care; frequency of BP monitoring; thresholds for reducing or stopping treatment; indications for referral to primary care for BP review; self-monitoring for symptoms Tell women they have an increased risk of developing hypertension and its complications in later life	Provide information to all women about signs and symptoms of pre-eclampsia with discharge instructions	Not specified	Inform women of increased risk of developing hypertensive disorders in future pregnancies and refer for review by a clinician with expertise in the management of HDP before embarking upon another pregnancy

	WHO (2011) (6)	ESC (2011) (5)	NICE (2011) (1)	ACOG (2013) (8)	SOGC (2014) (9)	SOMANZ (2015) (10)
Further investigation	Not specified	Not specified	If antihypertensive treatment is required beyond 6 weeks referral to hypertension specialist for investigation for secondary causes of hypertension is recommended If persistent proteinuria 3 months postpartum refer to nephrology	Not specified	Women with persistent postpartum hypertension should undergo the following tests ≥6 weeks postpartum: urinalysis; serum sodium, potassium and creatinine; fasting glucose and lipid profile; 12-lead ECG Refer to internal medicine / nephrology if resistant postpartum hypertension, or ongoing proteinuria or decreased eGFR 3-6 months postpartum	Women with persistent hypertension not previously should undergo routine work up according to standard regimens
Modifying future cardiovascular risk	Not specified	Lifestyle modifications, regular BP control, and control of metabolic factors are recommended	Advise women to achieve and keep a BMI within the healthy range before their next pregnancy (18.5–24.9 kg/m ²)	Yearly assessment of BP, lipids, fasting blood glucose, and BMI	Advise women to achieve and maintain a healthy BMI to reduce future pregnancy risk and improve long-term health Assess traditional cardiovascular risk markers Healthy diet and lifestyle	Lifestyle modification and optimisation of risk factors (especially in women who are obese, have cardiovascular risk factors, secondary hypertension or end organ disease)

1.8 Hypertensive disorders of pregnancy and long-term cardiovascular risk: epidemiology

Several large retrospective cohort studies have suggested that HDP are associated with an increased risk of future CVD in the mother. A study of 1.03 million women demonstrated an adjusted hazard ratio of 2.0 (95% confidence interval 1.7-2.2) for CVD in women with a history of gestational hypertension, pre-eclampsia, placental abruption or placental infarction (104). The association appears to be stronger for women with a diagnosis of pre-eclampsia as opposed to gestational hypertension (105), and stronger in women who have had more than one pregnancy complicated by hypertension (106). A systematic review (13 studies, n=21,030) examined the risk of future hypertension in women who had had pre-eclampsia in at least one pregnancy: the relative risk of chronic hypertension was 3.70, over a mean weighted follow-up period of 14 years (107).

A systematic review and meta-analysis of case-control and cohort studies (n= 116,175 women with pre-eclampsia or eclampsia; n=2,259,576 controls with normotensive pregnancies) demonstrated a significantly increased relative risk of CVD (RR 2.33) and cerebrovascular disease (RR 2.03), and a significantly increased cardiovascular mortality (RR 2.29) amongst women with a history of pre-eclampsia/eclampsia, positively correlated with the severity of pre-eclampsia/eclampsia (108). A small case-control study has suggested that healthy, normotensive women with a history of gestational hypertension have markers of endothelial dysfunction and early alteration of carbohydrate and lipid metabolism when compared with healthy, normotensive women with a history of previously normal pregnancy (109).

One retrospective cohort study also suggested an increased risk of future type 2 diabetes mellitus in women with previous HDP, and the same study reported an association between previous preeclampsia (both mild and severe) and future venous thromboembolism (106).

A recent prospective cohort study in the UK (n=1,105,568) followed-up parous women, without vascular disease at baseline, for 11.6 years. 26% of the study population reported a history of HDP. This was significantly more common among women with medicated hypertension at enrolment. In the whole population there were significantly increased risks of coronary heart disease (RR 1.29), ischaemic stroke (RR 1.29) and haemorrhagic stroke (RR 1.14) among women with a history of HDP. Strikingly this risk increase was substantially lessened, although not negated, if only women who were normotensive at enrolment were analysed. The authors suggest that therefore the major mechanism by which a hypertensive pregnancy confers additional long-term cardiovascular risk, may be by predisposing a woman to develop hypertension in middle age (110).

The severity of hypertension in later life has been associated with the degree of hypertension at six weeks postpartum (111). The nature of the relationship between BP control in the postnatal period and markers of vascular risk is unclear: it is uncertain if the correlation reflects increased severity of pathology conferring excess long-term risk, or BP control during the puerperium modulating future risk.

American Heart Association guidelines (2011) for the prevention of CVD in women cite a history of preeclampsia or gestational hypertension as a major risk factor for CVD, and advocate enquiring about pregnancy complications during the evaluation of an individual's CVD risk (112). However, despite a large body of epidemiological evidence underpinning this statement, it remains unclear what form screening should take in order to clarify an individual's risk. Routine use of novel biomarkers and modern cardiovascular imaging techniques (carotid intima-media thickness, cardiac magnetic resonance imaging and coronary artery calcium score) is as yet not supported by sufficient clinical evidence (113).

1.9 Self-management of blood pressure

1.9.1 'White coat' hypertension

The phenomenon of 'white coat' or 'office' hypertension has been recognised since the advent of ABPM and automated self-initiated HBPM. These terms refer to a group of patients who have an elevated BP when taken in the presence of a medical practitioner, but a normal BP in their home or work environment. The accepted definition is a SBP of >140mmHg, or >90mmHg on a conventional clinic measurement, but an average awake SBP <135mmHg and DBP <85mmHg on ambulatory BP monitoring (ABPM) (114).

Research has been done suggesting that white coat hypertension does present in pregnancy (115), and it has been suggested that ABPM (116) and HBPM (117) may help with the differentiation between 'white coat' and 'true' hypertension. However, a prospective observational study does highlight that women with a confirmed diagnosis of 'white coat' hypertension are at higher risk of developing gestational hypertension (40%) and pre-eclampsia (8%) (115).

1.9.2 Self-management of chronic hypertension in the general population

Previous work in the non-pregnant population has shown that HBPM and self-titration of antihypertensive medications in essential hypertension is both feasible, and more effective than usual care (118, 119). The TASMINH2 RCT (2010) demonstrated that self-management of BP in patients with poorly controlled essential hypertension resulted in a statistically significant reduction in mean SBP compared with patients undergoing usual care (difference at 12 months, -5.4mmHg, $p=0.0004$) (118). A further RCT in patients with high cardiovascular risk, TASMIN-SR (2014), has demonstrated an even greater effect of self-management in this cohort at 12 months (difference in SBP -9.2mmHg, 95% confidence interval -12.7 to -5.7) (119). No evidence to date suggests that this intervention should pose any risks to participants, or that BP control should be impaired through self-monitoring or self-management (118, 119).

HBPM has been shown to be more strongly related to indices of target organ damage (120) and to have better prognostic value in essential hypertension than office BP measurement (121). Voluntary HBPM by patients with essential hypertension is becoming increasingly common: recent surveys in UK primary care showed that 31% of patients used a home BP monitor, more common in patients under 60 (122), and that almost every GP had patients who self-monitor (123). A study comparing patient preference for different methods of measuring BP in essential hypertension showed HBPM to be the most acceptable (124). Both the European Society of Hypertension (125), ASH (126) and NICE (127) now recommend HBPM in the routine diagnosis and monitoring of essential hypertension.

American and European guidelines provide advice about how to undertake HBPM: They recommend taking 2-3 readings, with at least a one-minute interval between readings. They suggest taking readings both in the morning before taking medication, and at night before going to bed (125, 126).

1.9.3 Self-management of blood pressure in pregnancy

Women with medicated HDP would seem to be an ideal cohort in whom to apply self-management approaches: the disease has, in general, a limited time course meaning that intensive monitoring is more reasonable and adherence may be better. Pregnant women are in a younger age group than the majority of those with essential hypertension, and may be more comfortable with the use of technology to assist disease monitoring. Women might also be more empowered in the setting of a recent pregnancy to take greater responsibility for their health. The ASH states that 'HBPM is theoretically ideal for monitoring changes in BP during pregnancy', but notes that 'the extent to which it will improve the evaluation and management of hypertension during pregnancy has yet to be shown' (126).

A recent Australian survey about the accuracy of home BP monitors in pregnancy in one centre found that a wide range of devices are used, and although a minority had been formally validated (including the Microlife WatchBP® Home (128)), the majority (70-80%) were accurate to within

5mmHg (129). This was not a formal validation study (130) but was reassuring. In the past multiple oscillometric home BP monitors have failed formal validation in pregnancy and/or pre-eclampsia (131, 132).

Evidence exists to support the accuracy of HBPM in hypertensive pregnant women. Studies to date in antenatal women suggest a low non-concordance rate and a low rate of inaccurate recordings (133). Small studies (without formal controls) have also suggested: a better correlation between HBPM and indication of the need for antihypertensive medication (134); and a reduced number of hospital admissions in women with mild gestational hypertension who undertook HBPM (135).

An observational study, published only as a conference abstract, outlined the implementation of a postnatal HBPM intervention in women with pre-eclampsia, gestational or chronic hypertension (n=370). They used a wrist BP monitor (Omron-RX wrist monitor) and had these readings reviewed regularly by a specialist midwife who advised on medication alteration and discontinuation based on an algorithm. Persistent hypertension was identified in a significant proportion of women: 55 women were referred to specialist care at 12 weeks (136). This study did not have a control group, so does not provide any evidence of greater effectiveness than standard care, and the BP monitor used in this study has not been validated for use in pregnancy. More recent, non-randomised evaluations of remote monitoring of HDP, during pregnancy and postpartum, have suggested this approach might be feasible and acceptable amongst this population (137, 138).

During the CHIPS (Control of Hypertension in Pregnancy Study) pilot study, 132 women were sent postnatal questionnaires. 126 questionnaires were completed and 84/126 (67%) reported using a home BP monitor (139). Although there are inherent biases in this sample, and these are non-UK data, compared to observational data from the general population, this figure is strikingly high, and echoes that reported in the adult population with essential hypertension (122). The academic community have a responsibility to evaluate the efficacy of this intervention, and if appropriate produce evidence-based recommendation for its use in this population (140).

A pilot RCT was conducted to evaluate the role of HBPM in reducing the number of scheduled antenatal visits, at a time when these were scheduled fortnightly from 28 to 36 completed weeks and then weekly until delivery. Women in this study expressed a preference for HBPM with a reduced visit schedule, and there was no significant difference in anxiety scores between the two groups (141), suggesting HBPM might be acceptable to women. ABPM has been demonstrated to improve identification of patients at high risk of an adverse outcome when compared to conventional sphygmomanometry performed in the clinic setting (142). However, evidence suggests that pregnant women find HBPM more acceptable than ABPM (143).

If patients were undertaking HBPM, then the option of testing a self-management intervention as per the TASMIN studies might be appropriate within certain safety constraints. This would potentially have positive implications in terms of patient empowerment, cost and time saving and BP control. BP control in the postpartum period can be challenging due to other pressures on women and healthcare professionals, and as a result of the need to wean medication appropriately in response to changing BP over a relatively short time-frame. If self-management in the postpartum period proved to be a feasible, acceptable and a successful strategy for management of BP, it could lead to a reduction in the length of inpatient stay, readmissions and the number of postpartum visits, with cost-saving implications for both primary and secondary care. Currently in women with a diagnosis of pre-eclampsia, NICE recommends BP monitoring daily or on alternate days for two weeks after discharge from hospital (section 1.7.3) (1). Furthermore, as BP in the immediate postpartum period has been shown to correlate with essential hypertension in later life (111), any strategy, which successfully increases women's adherence to an effective treatment regimen, has the potential to influence their healthcare needs well into the future.

One concern about self-management approaches in clinical practice has been evidence suggesting diminishing adherence to the intervention over time (144). In the majority of women with HDP, BP is expected to normalise over a period of weeks to months (section 1.7.1), and therefore the self-

management intervention is only required to be relatively short-lived, which may assist the adoption and maintenance of the intervention.

1.9.4 Telemonitoring

All developed countries' health systems are currently seeking to harness digital technology, as it is perceived as offering cost-effective (145), scalable, patient-centred tools (146), which can support self-management of disease, at a time when health services worldwide are coming under increasing pressure from demographic and economic challenges (147). The intelligent use of health technology is a key element of the Department of Health's 'Five Year Forward View' (2014) (148). They aim to 'exploit the information revolution' to empower patients and give them access to better information about their healthcare. The National Information Board has been established by the Department of Health, and they plan to create 'an expanding set of NHS accredited health apps that patients will be able to use to organise and manage their own health and care' (149).

Telemonitoring is defined as 'the use of information technology to monitor patients at a distance' (150). The potential for rapid shifts in medication requirement during the puerperium mean that support for self-management via telemonitoring is attractive. Telemonitoring can utilise landlines, the internet (151), SMS (short message service) (150) or smartphones (140). To date telemonitoring has largely employed SMS systems, and this was effective in many cases, including in the management of essential hypertension (152) and heart failure (153).

Since the advent of the first app-ready smartphone a decade ago (154), their use has increased at an extraordinary rate: according to the Ofcom 'Adults' Media Use and Attitudes' survey in 2013 62% of adults in the UK were using a smartphone (155). This had risen to >70% by 2015 (156), and 81% by May 2016 (157). Use is higher in younger people: in 2015 amongst 16-24 year-olds usage was 93%, and 82% amongst 25-34 year-olds (158). There has simultaneously been a proliferation of health and medical apps, thought to number over 100,000 in 2014 (159), which now present an attractive and possibly more engaging solution to supporting the self-management of disease. However, the high

level of smartphone uptake and wide range of available medical apps, are in contrast to the tiny proportion of patients (2%) who report any digitally enabled transaction with the NHS (149).

There is public and patient enthusiasm for telehealth solutions: a survey (n=7000) conducted by the website www.patient.co.uk/ (2012) reported that 60% would like to monitor their chronic health condition using a mobile app (160). A service development program recently examined patient satisfaction with using an interactive, smartphone-based, remote blood glucose monitoring system designed for women with gestational diabetes (GDm-health). Questionnaires were received from 49/52 women, and suggested they found the technology acceptable and convenient (161).

This project proposes utilising both SMS and smartphone app technology to support a novel complex intervention for postpartum BP self-management (section 1.11). Allowing women to not only measure their own BP at home, but also to submit the readings to a central server and receive immediate, individualised responses might serve to empower patients even further, and allow them to better engage with their health condition.

1.10 Implementation of self-management interventions

Self-management approaches have been demonstrated to be beneficial to multiple stakeholders, and can be cost effective (118, 119, 162). However, a key element in the implementation of health technology is ensuring successful adoption. Technology is a means to an end: its efficacy is intrinsically linked to the willingness and ability of the end-users (both health care professionals and patients alike) to utilise it as an efficient tool in patient care.

NHS England, in collaboration with the US Department of Health and Human Services, published a report (2016) looking at factors influencing the successful adoption of digital health and care record systems (163). They found evidence that successful adoption was more likely if digital systems were designed with specific clinical areas in mind, or to improve clinical practice in the treatment of a given condition. Furthermore, clinicians' need for certain applications should drive specification of

digital systems. This report acknowledges that barriers to implementation may lie in the leadership and culture of an organisation, how the organisation functions, in the individuals utilising the technology or in the technology itself. The most significant barriers are usually associated with people and cultural issues, as opposed to the technology.

The Nuffield Trust released a research summary (2016) examining how best to deliver the potential benefits of digital health care. They clearly state that technology needs to be well designed to make healthcare professionals' jobs, or the patient's interaction easier. They emphasise that, at its core, this will involve reimagining existing work processes, such that technology does not become an additional layer to the existing workload. They identify seven opportunities that digital health care can exploit to improve productivity and care quality (Figure 4) (164). This report also reiterates the point made by the collaboration between NHS England and the US Department of Health and Human Services (163), that cultural change is essential.

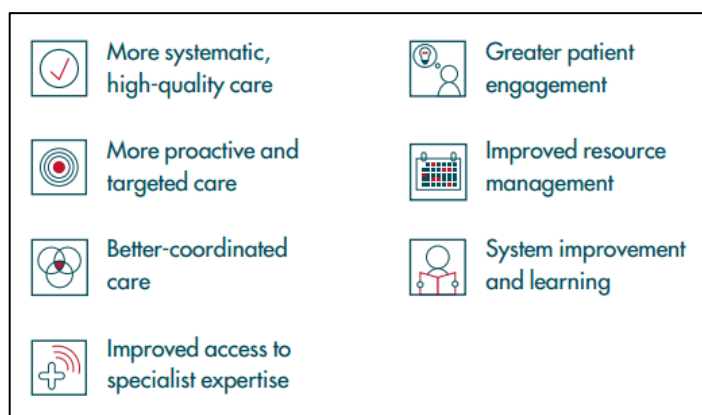


Figure 4: Opportunities for digital health care to improve productivity and care quality (copied from Nuffield Trust 'Delivery the benefits of digital health care' 2016) (164)

The Medical Research Council first published a framework for the development of complex interventions in healthcare in 2000 (165), which was updated in 2008 (166). They recommend that a good theoretical understanding is required of how the intervention causes change, and that a thorough process evaluation is needed to identify implementation problems. Sample sizes may need to be larger to take account of greater variability in individual level outcomes and a single primary

outcome may not be appropriate – a range of measures will likely be required in order to assess efficacy and explore unintended consequences. Additionally they recommend allowing for a specified degree of adaptation to local circumstances.

A review of ‘multiple forms of innovation implementation’ (2013) identified that the complex process through which innovations are implemented within an organisation is often treated as a ‘black box’. The authors express the view that this overlooks the opportunity to examine how an innovation is implemented, a factor critical to the success of any intervention (167). Research studies from healthcare, and telemedicine in particular often focus on interventions once they have been in place for some time, citing that organizational and professional issues often do not emerge when interventions are experimental, or being piloted (168, 169). However, there may be a role for exploring all stages of implementation, from planning through to reflection after large-scale roll out. A review of 100 RCTs suggested that typically associated qualitative work was uncommon, often conducted before the trial took place, and rarely used to understand trial results. This review highlighted significant methodological flaws and poor integration (170).

Normalisation Process Theory (NPT) is a theoretical model introduced to help understand the processes by which practices are implemented, embedded and integrated into their social contexts, such that a practice becomes, and is sustained as, a routine element of everyday work (171). The different components of NPT are as follows: routine embedding occurs as a result of people working, collectively and individually, to implement a practice; implementation is operationalised through coherence, cognitive participation, collective action and reflexive monitoring; the production and reproduction of a material practice requires continuous investment to sustain the integration of a practice in its social contexts (171). When implementing a novel complex intervention into everyday work, such as self-management of BP into postnatal clinical care, the ideal scenario is that the intervention becomes a routine component of normal practice. Assessing why this does, or does not happen, is of substantial importance. If NPT is considered during the design and development phase

of a complex intervention, and during its evaluation, this may improve both trial design and implementation potential (172).

Historically quantitative and qualitative research methods have often been viewed as incompatible, potentially because of their very different epistemological underpinnings (173), and divergent purposes (174). However, increasingly there have been calls to see these methodologies as complementary in health services research (175-177). Some commentators have even gone so far as to state that the strengths of one approach might compensate, at least in part, for the weaknesses of the other (178). Four models by which qualitative and quantitative research methodologies may be integrated have been proposed (Figure 5) (178).

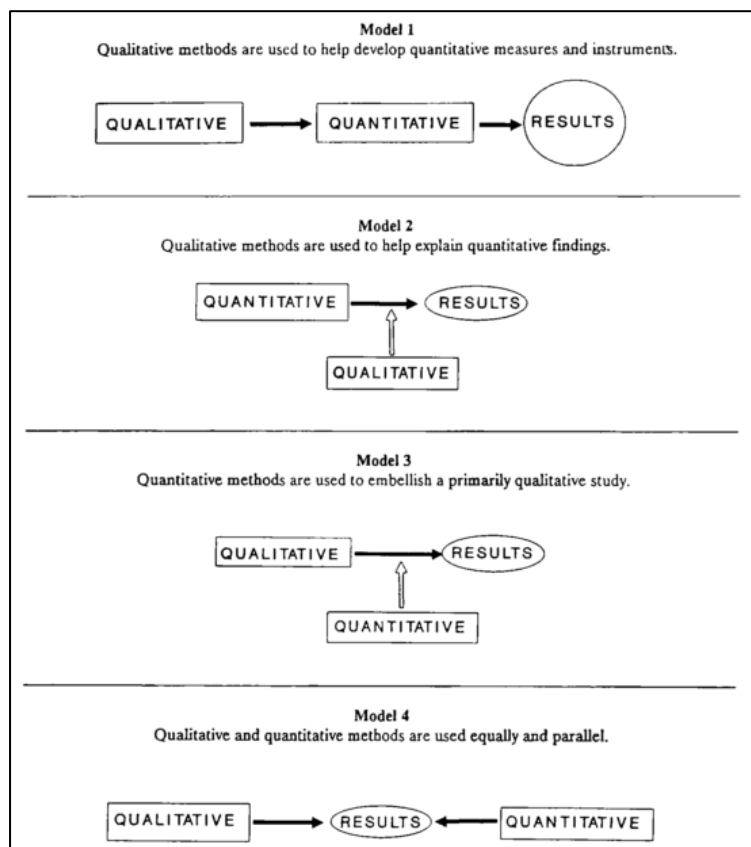


Figure 5: Four possible ways that qualitative and quantitative methods might be integrated (copied from Steckler *et al.* 1992) (178)

In this study (Chapter 4) the second of these models was selected (Figure 5) whereby the evaluation is predominantly quantitative and qualitative results were utilised to help understand and explain the quantitative findings (Chapter 5) (178). The aim was to explore elements influencing the successful or unsuccessful implementation of a novel self-management intervention for postpartum antihypertensive adjustment. Audio-recorded, semi-structured, qualitative interviews were undertaken with participants who undertook self-management and usual care (Chapter 5). This qualitative data was utilised to evaluate patient views of self-management of BP postpartum in order to identify common themes of critical factors that affect successful and unsuccessful implementation of technology-based self-management solutions in the NHS.

1.11 Research questions

What evidence exists regarding the optimal approach to management of hypertensive disorders of pregnancy postpartum (Chapter 2)?

A systematic review was undertaken of the management of hypertension postpartum intending to highlight all available evidence for different management strategies in order to allow design of a better-informed RCT.

How do healthcare professionals currently approach the adjustment of antihypertensive medications postpartum (Chapter 3)?

A local audit was conducted to explore adherence to NICE guidance, and to estimate the proportion of women being discharged home after birth on antihypertensive treatment. In view of the absence of robust evidence-based guidance, and to ensure avoidance of imposing a strategy at odds with routine practice in the local area, a regional survey of healthcare professionals was conducted to establish usual clinical practice and inform standardised design of medication adjustment schedules for antihypertensive medication in the postpartum period.

Is it feasible to develop a novel, efficacious self-management intervention for postnatal hypertension for use in a multi-centre randomised controlled trial (Chapter 4)?

The mainstay of this project was development and initial evaluation of a novel self-management intervention for postnatal hypertension. This utilised validated home BP monitors, individualised medication adjustment schedules and a customised telemonitoring system. In line with guidance from the Medical Research Council, regarding development of complex interventions, this was evaluated in a pilot study (166): self-management of postnatal antihypertensive treatment was compared to usual care in a pilot multi-centre RCT. The primary outcome was to test the feasibility of the proposed methods and procedures, as recommended in published guidance for pilot studies (179, 180). This aimed to inform planning of a large-scale multi-centre RCT, where the primary

objective will be to determine whether self-management can improve BP control in women with medicated HDP postpartum.

Is self-management of blood pressure postpartum acceptable to patients when compared to usual care (Chapter 5)?

Structured qualitative interviews were conducted during the pilot study with participants from both groups. This will enable assessment of whether patients are happy to employ self-management techniques during the postnatal period, and help design of the most user-friendly self-management solution. The views of patients regarding self-management and use of technology in healthcare, and in contrast their views of usual postpartum BP management by general practitioners (GPs) and community midwives, are vital to successful implementation.

Are markers of long-term cardiovascular risk influenced by blood pressure control postpartum (Chapter 6)?

Given the possible connection between postnatal BP control and long-term cardiovascular risk, the study population was utilised to carry out an embedded sub-study to assess markers of vascular risk in both groups. This was a pilot study, but in a future large-scale trial, the baseline characteristics of the two randomised groups should be similar, so if improved BP control was demonstrated with the intervention, this would allow analysis of whether BP control postpartum directly influenced markers of vascular risk. This would help to determine if it is the severity of pathology or effectiveness of control, or both, that influences long-term outcome.

Chapter 2: Systematic review of the management of hypertensive disorders of pregnancy in the postpartum period

2.1 Overview

This chapter reports a systematic review of the management of hypertension postpartum in women with HDP, intending to highlight all available evidence for different management strategies in order to allow design of a better-informed clinical trial. The survey was published in the BMJ Open in December 2017 (Appendix 1) (181).

2.2 Objectives

Prior to developing and testing a self-management intervention for antihypertensive adjustment postpartum (Chapter 4), this systematic review aimed to establish what evidence already exists to guide the optimal approach to management of gestational hypertension and pre-eclampsia during the postnatal period. The intention was to gain a broad and thorough understanding of all therapeutic interventions (not limited to antihypertensive medications), which have previously been evaluated in this population. Furthermore, the hope was to establish whether an evidence base exists for BP thresholds for medication adjustment, or specific choice of antihypertensive agent, which could be utilised in the development of a self-management algorithm for antihypertensive down-titration postpartum.

The specific research questions were:

- [1] How should BP be monitored in women with HDP postpartum?
- [2] What BP thresholds should be used for antihypertensive treatment initiation, adjustment and cessation postpartum?
- [3] Which antihypertensive medications should be used during the postnatal period?
- [4] What are the benefits and harms of other therapeutic interventions for women with HDP postpartum?

2.3 Methods

2.3.1 Prospective registration and reporting

A protocol, with explicitly defined objectives, study selection criteria, and approaches to assessing study quality, outcomes and statistical methods, was developed (Appendix 2) and prospectively registered with PROSPERO: International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015015527). The guidelines for meta-analyses and systematic reviews outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement were followed (Appendix 3) (182).

2.3.2 Data sources and searches

A systematic literature review was undertaken aiming to capture evidence regarding postpartum management of HDP (Appendix 2). The following databases were searched, from inception to 16/03/2017: Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Medline, PsycINFO, Science Citation Index, Science (Web of Science Core Collection), Social Science Citation Index & Conference Proceedings Citation Index. The Medion database was searched at the initial planning stage in October 2014 but was unavailable at the time of the final search. Reference lists were hand-searched and relevant experts were contacted for potentially relevant studies, which might have been missed by electronic searches (183).

2.3.3 Criteria for considering studies for this review

2.3.3.1 Types of studies

No date or language restrictions were imposed but only human studies were considered. RCTs, quasi-randomised studies, cohort studies (prospective and retrospective) and case-control studies were included. Guidelines, reviews, expert opinions, letters, commentaries, audits, case series and

case reports were excluded. Consistent with guidance from Cochrane, conference abstracts were included (92).

2.3.3.2 *Types of participants*

Studies where all or part of the population consisted of postnatal women with HDP were included.

Where the population was exclusively antenatal or intrapartum the study was excluded.

2.3.3.3 *Types of interventions*

All therapeutic interventions for the management of hypertension were considered: medical, surgical and organisation of care. Studies where the intervention specifically targeted treatment of HELLP syndrome (haemolysis, elevated liver enzymes and low platelets) or the prevention or management of eclampsia were excluded, as were interventions focused on prevention of postpartum hypertension, or choice of anaesthetic or sedative in pre-eclampsia. Only studies where a control group was used were included. The control group could receive an alternative intervention, placebo or no intervention.

2.3.4 *Study selection*

Two reviewers independently screened the titles and abstracts, and then critically reviewed the full text of selected studies to assess eligibility. Discrepancies were resolved by discussion.

2.3.5 *Data extraction and quality assessment*

Where more than one report was published about a single study, these were reviewed separately but data were grouped in the analysis. When data was missing from a report (for example the sole publication was a conference abstract), or where the population was mixed (antenatal and postpartum), authors were contacted directly to request further detail. The response rate to these emails was low. Where possible only data for postnatal women with HDP has been included, and when it was not possible to subdivide the data this has been explicitly stated.

Two reviewers independently extracted data. Information collected from each study included study design, setting, participants, and outcomes. For trials with multiple intervention arms, data were extracted from eligible comparison arms. Data were extracted for the primary and secondary outcomes outlined in Table 4.

Table 4: Outcome measures

	Outcome measures	Timing
Primary outcome(s)	Maternal mortality Maternal morbidity (ischaemic stroke, intracranial haemorrhage, eclamptic seizure; development of preeclampsia with severe features; postnatal complication requiring intervention) Systolic blood pressure control Diastolic blood pressure control Mean arterial pressure control Safety data (adverse events or maternal side effects)	Direct maternal deaths up to day 42 postpartum; late maternal deaths up to 1 year postpartum
Secondary outcome(s)	Critical care admission Length of hospital stay following delivery Postnatal readmission to secondary care Antihypertensive medication requirement Urine output Laboratory values Other as defined by study	

Two reviewers independently assessed each trial's methodological quality using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials (184), including approach taken to minimise bias due to selection, performance, detection, attrition, and reporting. For the assessment of bias in cohort and case-control studies the Newcastle-Ottawa scale was used (185). A global assessment of bias across trials was made.

2.3.6 Data synthesis and analysis

Due to the heterogeneous nature of these studies a narrative synthesis was undertaken. No subgroup analysis was planned.

2.4 Results

2.4.1 Search results

Our searches yielded 7,105 records and after excluding duplicate records, 4,561 titles and abstracts were screened (Figure 6). Two reviewers evaluated 80 potentially relevant articles. Forty-five articles, representing 39 studies (32 randomised trials, two prospective cohort studies, and five retrospective cohort studies) reporting data from 2,901 postnatal participants met the inclusion criteria (Table 5). Thirty-three were excluded (Table 6). 9/39 (23%) were published only as conference abstracts. No further details were available following author contact.

2.4.2 Characteristics of included studies

A range of interventions were assessed including antihypertensive medications (18 studies, 982 participants), loop diuretics (four studies, 503 participants), parenteral steroids (one study, 157 participants), other medications (six studies, n=188), uterine curettage (eight studies, 837 participants) and novel models of care (two studies, 234 participants). Two studies included more than two hundred participants (186, 187), four were from lower-middle-income settings (186, 188-190) (classified according to the United Nations (191)), and 13/39 (33%) had follow up periods longer than seven days (Table 5).

Only 5/39 (13%) and 7/39 (18%) studies, respectively, reported maternal mortality or major maternal morbidity (for definition see Table 4, and expanded for each study in Table 5) (Table 9 and Table 10). Whilst the majority of studies did report some measure of BP control, three did not (Table 9 and Table 10). Nineteen studies (49%) reported safety data – side-effects and harms resulting from the intervention (Table 9 and Table 10).

Five studies (13%) – all evaluating antihypertensive medications – involved mixed antenatal and postnatal populations (188, 192-195). Authors were contacted to request their dataset for the postnatal participants, but none were received. Six studies (15%) included participants with chronic hypertension alongside women with de novo HDP (193, 194, 196-202). Twelve studies (31%) included women with eclampsia – in one all participants were eclamptic (Table 11) (188).

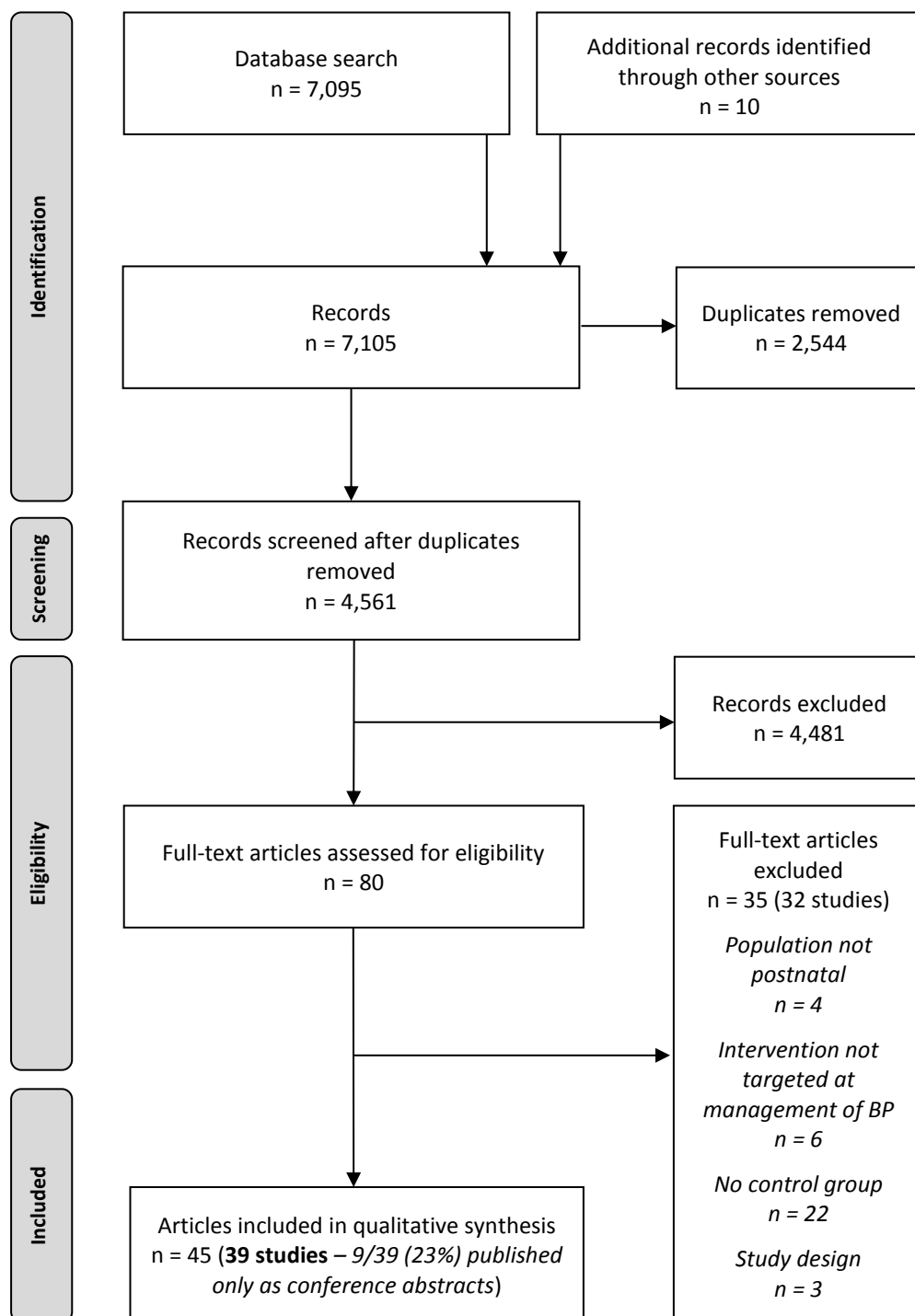


Figure 6: PRISMA Flowchart

Table 5: Characteristics of included studies (n=39)

Author and year	Methods		Participants			Intervention			Outcomes	
	Study design	Duration	n*	Age /y†	Setting	Country	Intervention	Control(s)	Primary	Secondary
ANTIHYPERTENSIVE MEDICATIONS (18 studies)										
Calcium channel blockers										
Barton 1990 (203)	RCT	Enrolled immediately after birth F/U 48h	31	24.0 26.3	Tertiary referral hospital	USA	Nifedipine 10mg PO 4-hourly for 48 hours	Placebo	MAP	SBP, DBP Maternal heart rate AHT requirement Urine output Laboratory values (urine protein, creatinine clearance, HCT, plt, ALT, BUN, creatinine, serum electrolytes, UA, urine specific gravity)
Vermillion 1999 (192)	RCT	Enrolled within 24h of birth F/U 3 – 24h	21	27.2±7.3 27.0±6.4	Tertiary referral hospital	USA	Nifedipine 10mg stat PO then 20mg every 20min until BP <160/110mmHg or max 5 doses + IV placebo	Labetalol 20mg, then 40mg, then 80mg IV every 20min until BP <160/110mmHg or max 5 doses (300mg) + PO placebo	SBP + DBP	SBP (failure to achieve target <160mmHg) DBP (failure to achieve target <110mmHg) Maternal side effects AHT requirement Urine output
Sayin 2005 (204)	RCT	Enrolled 24h after birth F/U 72h after BP controlled	83	17-41	Tertiary referral hospital	Turkey‡	Nifedipine 10mg PO QDS until BP <150/100mmHg for 48h	Methyldopa 250mg PO TDS	SBP + DBP	Maternal mortality AHT requirement Hypertensive retinopathy

Abbreviations: AHT = antihypertensive; ALT = alanine aminotransferase; BD = twice daily; BP = blood pressure; BUN = blood urea nitrogen; DBP = diastolic blood pressure; F/U = follow-up; IM = intramuscular; IV = intravenous; MAP = mean arterial pressure; plt = platelets; PN = postnatal; OD = once daily; PO = oral; QDS = four times daily; RCT = randomised controlled trial; SBP = systolic blood pressure; S/L = sublingual; TDS = three times daily; UA = uric acid

* n = postnatal population (antenatal excluded)

† Where separate data available for study groups, intervention group listed first

‡ Non-English language manuscript

Author and year	Methods		Participants			Intervention			Outcomes	
	Study design	Duration	n ⁺	Age /y ⁺	Setting	Country	Intervention	Control(s)	Primary	Secondary
Vasodilators										
Palot 1979 (205)	Retrospective cohort study	Not specified	54	24.5 (17-37)	Not specified	France ⁺	Hydralazine 5mg IV stat then 1% IV infusion, furosemide 20mg IV stat and 30% hypertonic glucose	(1) Clonidine IV and furosemide 20mg IV stat Or (2) Non-systematic treatment	Maternal morbidity (development of pre-eclampsia with severe features)	BP (time to resolution of hypertension)
Griffis 1989 (206, 207)	RCT	F/U 24h	26	Not specified	Tertiary referral hospital	USA	Hydralazine 20mg IM QDS for 24h	Methyldopa 250mg IV QDS x 24h	MAP	Maternal side effects AHT requirement Urine output (time to diuresis)
Walss Rodriguez 1991 (208)	RCT	Not specified	38	16-40	Not specified	Mexico ⁺	Hydralazine 40mg PO QDS, duration not specified; if DBP >110mmHg PRN nifedipine 10mg SL every 30min, to max 3 doses	Nifedipine 10mg SL every 30min if DBP ≥110mmHg	SBP	DBP AHT requirement
Begum 2002 (188)	Quasi-randomised trial	Not specified	15	24.09±4.93 22.72±5.08	Tertiary referral hospital	Bangladesh	Hydralazine 5mg then 2mg IV bolus every 15min until DBP 90-95mmHg	Hydralazine 20mg/200ml normal saline IV infusion; 10 drops per min, increased by 5 drops at 15min intervals; until DBP 90-95mmHg	DBP	Maternal side effects AHT requirement Maternal heart rate
Vigil-De Gracia 2007 (209)	RCT	Enrolled day 2-3 after birth F/U not specified	82	29.9±5.9 31.3±5.5	Tertiary referral hospital	Panama	Hydralazine 5mg IV every 20min until BP <160/110mmHg or max 5 doses	Labetalol 20mg, then 40mg, then 80mg IV every 20min until BP <160/110mmHg or max 5 doses (300mg)	SBP + DBP	Maternal mortality Maternal morbidity (development of pre-eclampsia with severe features) Maternal side effects AHT requirement Maternal heart rate
Hennessy 2007 (194)	RCT	F/U 3h	37	21-43 (mean 33)	Tertiary referral hospital	Australia	Diazoxide 15mg IV every min, maximum dose 300mg	Hydralazine 5mg IV every 2min, maximum 15mg	SBP + DBP	SBP (10mmHg above target after 1 hour) DBP (10mmHg above target after 1 hour) Maternal side effects (including hypotension) Time taken to administer drug

Author and year	Methods		Participants			Intervention			Outcomes	
	Study design	Duration	n*	Age /y†	Setting	Country	Intervention	Control(s)	Primary	Secondary
Beta blockers										
Fidler 1982 (210)	RCT	Enrolled 4 days after birth F/U 9 days	80	29.7±1.0 27.8±0.9	Tertiary referral hospital	UK	Timolol 5mg PO TDS for 9 days	Methyldopa 250mg PO TDS for 9 days	DBP	SBP DBP (time to achieve control, proportion achieving control) Maternal side effects
Garden 1982 (195)	RCT	Enrolled immediately after birth F/U 45-64h	6	25-44 20-28	Tertiary referral hospital	South Africa	Labetalol 200mg/200ml 5% dextrose, 20mg/h IV infusion, doubled every 30min until DBP <100mmHg or maximum dose 160mg/h	Dihydralazine 100mg/200ml 5% dextrose, 10mg/h IV infusion, doubled every 30min until DBP <100mmHg or maximum dose 80mg/h	DBP	Maternal side effects
Mabie 1987 (193)	RCT	Enrolled 1-96 hours after birth F/U 3h	41	23.7±6.9 22.9±7.0	Tertiary referral hospital	USA	Labetalol 20mg IV every 10min then escalating until DBP <100mmHg or maximum cumulative dose reached (300mg)	Hydralazine 5mg IV every 10min until DBP <100mmHg	MAP	MAP (time to maximal decrease) DBP (achieving target <100mmHg) Maternal side effects AHT requirement Maternal heart rate
Sharma 2016 (198)	RCT	F/U not specified (but >24h)	50	Not specified	Tertiary referral hospital	USA	Labetalol 200mg PO BD	Nifedipine XL 30mg PO OD	SBP + DBP	Maternal side-effects Length of PN hospital stay AHT requirement
Shumard 2016 (211)	Retrospective cohort study	F/U not specified (but >24h)	128	Not specified	Not specified	USA	Labetalol PO (variable dose and frequency)	Nifedipine PO (variable dose and frequency)	Length of hospital stay after birth	SBP, DBP AHT requirement
Other										
Gaisin 2013 (196)	RCT	6 months	30	23-29	Not specified (hospital)	Russia	Indapamide 1.5mg PO OD, duration unclear	Adjusted dose methyldopa	SBP + DBP	Safety data Laboratory values (lipid and glucose metabolism) Adherence to treatment Weight reduction Decrease in albuminuria Decrease in LV mass index Endothelial function Milk production

Author and year	Methods		Participants			Intervention			Outcomes	
	Study design	Duration	n*	Age /y†	Setting	Country	Intervention	Control(s)	Primary	Secondary
Gaisin 2014 (212)	RCT	1 year	30	24-28	Not specified (hospital)	Russia	Indapamide 1.5mg PO OD with ursodeoxycholic acid 250mg PO TDS, duration unclear	Adjusted dose methyldopa	SBP + DBP	Maternal side effects Laboratory values (atherogenic lipid profile, glucose metabolism, renal function) Offspring adverse events Weight reduction Decrease in microalbuminuria Decrease in LV mass index Endothelial function
Krebs A 1956 (213, 214)	Retrospective cohort study	F/U not specified (but >24h)	140	Not specified	Not specified	Switzerland†	Reserpine 0.25mg PO or IM TDS or QDS for 7 days	Phenobarbital	SBP + DBP	SBP + DBP (non-responders) Maternal side effects Resolution of albuminuria Resolution of oedema
Katz 2015 (201, 202)	RCT	F/U not specified	90	Not specified	Tertiary referral hospital	Brazil	Clonidine 0.1mg PO repeated every 20min to maximum 6 doses	Captopril 25mg PO repeated every 20min to maximum 6 doses	SBP + DBP	SBP (% reduction) SBP + DBP (daily mean) Maternal side effects AHT requirement
LOOP DIURETICS (3 studies)										
Matthews 1997 (215)	RCT	Enrolled 12-24h after birth F/U 6 weeks	19	Not specified	Tertiary referral hospital	UK	Furosemide 40mg PO OD for 7 days	Placebo	MAP	Length of PN hospital stay AHT requirement Urine output Laboratory values (hypokalemia)
Ascarelli 2005 (187)	RCT	Enrolled 2-24h after birth F/U 6 weeks	264	22.8±6.1 22.9±6.0	Tertiary referral hospital	USA	Furosemide 20mg PO OD + potassium 20mEq PO OD for 5 days	No intervention	SBP	Maternal morbidity (postnatal complication requiring intervention) DBP Length of PN hospital stay AHT requirement Maternal weight Maternal HR Duration of magnesium sulphate

Author and year	Methods		Participants			Intervention			Outcomes	
	Study design	Duration	n*	Age /y [†]	Setting	Country	Intervention	Control(s)	Primary	Secondary
Amorim 2015 (216)	RCT	Enrolled immediately after birth F/U 5 days	120	Not specified	Tertiary referral hospital	Brazil	Furosemide 40mg PO OD, duration not specified	Placebo	SBP + DBP	MAP SBP (daily episodes ≥180mmHg) DBP (daily episodes ≥110mmHg) Length of PN hospital stay AHT requirement Urine output Maternal heart rate
Veena 2017 (190)	RCT	Enrolled <24h after birth	100	24.34±4.31 24.02±4.27	Tertiary referral hospital	India	Furosemide 20mg PO OD + nifedipine 10mg PO TDS for 3 days	Nifedipine 10mg PO TDS for 3 days	SBP + DBP	MAP Maternal morbidity (postnatal complication requiring intervention) Length of hospital stay after birth Antihypertensive medication requirement Urine output
OTHER DRUGS (7 studies)										
Selective 5-HT antagonists										
Weiner 1982 (217)	RCT (crossover)	F/U not specified	5	Not specified	Tertiary referral	USA	R41468 IV (dose not specified) bolus then infusion for 90min	Placebo	MAP	MAP (rate at which hypertension returned post-infusion) Urine output (infusion related diuresis)
Weiner 1984 (218)	RCT (crossover)	Enrolled immediately after birth F/U 3.5h	20	28±6.4	Tertiary referral	USA	Ketanserin 10mg IV bolus then 4mg/hr IV infusion. Repeat bolus after 5min if no response.	Placebo	SBP + DBP	Maternal side effects DBP (target <95mmHg) MAP AHT requirement Response rate
Montenegro 1985 (219)	RCT (crossover)	Enrolled immediately after birth F/U not specified	30	21.5 (13-31)	Tertiary referral hospital	USA	Ketanserin 10mg IV bolus, repeated if no response. If no response to second bolus IV infusion 4mg/hr (increments of 2mg/hr every 10min to max 12mg/hr).	Placebo	MAP	Maternal side effects

Author and year	Methods		Participants			Intervention			Outcomes	
	Study design	Duration	n*	Age /y [†]	Setting	Country	Intervention	Control(s)	Primary	Secondary
Alternative therapies										
Hladunewich 2006 (220)	RCT	Enrolled immediately after birth F/U 10 days	45	29±6 28±7	Tertiary referral hospital	USA	L-arginine 3.5g PO QDS or 10g IV TDS for 3-9 days	Placebo	MAP	Maternal side effects SBP, DBP AHT requirement Laboratory values (glomerular filtration rate (GFR) (inulin clearance), Albumin/creatinine (A/C) ratio, vasoactive hormones (NO and cGMP), liver function tests (LFTs), plt) Renal plasma flow (para-amino hippurate clearance), renal blood flow = renal plasma flow / (1-HCT), renovascular resistance
Liu 2009 (221)	Quasi-randomised trial	Enrolled day 2 after birth F/U 3 weeks	72	26.6±3.7 25.7±3.9	District general hospital	China [†]	Shengkangbao 10g PO or IV BD for 3 weeks	No intervention	Percentage of cases with positive albuminuria	SBP, DBP Laboratory values (24h urinary albumin, plasma total protein, plasma albumin, urinary albumin negative inversion rate, renal function)
Steroids										
Barrilleaux 2005 (222, 223)	RCT	Enrolled immediately after birth F/U 4.5 days	157 (175)	24.5±6.8 23.9±6.4	Tertiary referral hospital	USA	Dexamethasone 10mg x 2, then 5mg x 2 IV BD for 48 hours	Placebo	Antihypertensive medication requirement	MAP Critical care admission Length of PN hospital stay Urine output Laboratory values (plt, lactate dehydrogenase (LDH), aspartate aminotransferase (AST)) Stay in recovery >24h
Atrial natriuretic peptide										
Shigemitsu 2015 (224)	Retrospective cohort study	F/U not specified	16	Not specified	Tertiary referral hospital	Japan	Carperitide (no further details)	Standard care	MAP	Maternal mortality Maternal side effects Need for dialysis Time to diuresis
UTERINE CURETTAGE (8 studies)										
Salvatore 1967 (225)	Prospective cohort study	Enrolled immediately after birth F/U 10 days	48	16-45	Tertiary referral hospital	Brazil ^{††}	Uterine curettage	No intervention	SBP + DBP	Maternal morbidity (development of pre-eclampsia with severe features – seizures)

Author and year	Methods		Participants			Intervention			Outcomes	
	Study design	Duration	n ^a	Age /y ^b	Setting	Country	Intervention	Control(s)	Primary	Secondary
Magann 1993 (226)	RCT	Enrolled immediately after birth F/U 24h (telephone at 7 weeks)	32	22.9±5.6 23.4±6.6	Tertiary referral hospital	USA	Uterine curettage	No intervention	MAP	Maternal side effects Length of PN hospital stay AHT requirement Urine output Laboratory values (HCT, plt, AST, LDH)
Magann 1994(227)	RCT	Enrolled immediately after birth F/U 48h (telephone at 7 weeks)	45	22.3±6.4 22.8±6.6 22.8±6.1	Tertiary referral hospital	USA	Uterine curettage	(1) Nifedipine PO OR (2) Usual care	MAP	Maternal side effects Urine output Laboratory values (HCT, plt, AST, LDH)
Gocmen 1996 (228)	Prospective cohort study	Enrolled immediately after birth F/U 24h	50	Not specified	Tertiary referral hospital	Turkey ^c	Uterine curettage	No intervention	MAP	Urine output Laboratory values (plt)
Gomez 2005 (229)	RCT	Enrolled immediately after birth F/U not specified	86	Not specified	Tertiary referral hospital	Peru	Uterine curettage	No intervention	MAP	Maternal side effects Length of PN hospital stay AHT requirement Urine output
Alkan 2006 (230)	RCT	Enrolled immediately after birth F/U 24h	56	22.8±3.4 24.6±7.5	Tertiary referral hospital	Turkey	Uterine curettage	No intervention	MAP	Maternal side effects Urine output Laboratory values (plt, LDH, AST, ALT)
Ragab 2013 (186)	RCT	Enrolled immediately after birth F/U 96h	420	Not specified	Tertiary referral hospital	Egypt	Uterine curettage	No intervention	MAP	Maternal mortality Maternal morbidity (development of pre-eclampsia with severe features) MAP (time to MAP ≤105mmHg) Urine output Laboratory values (creatinine, plt, UA)
Mallapur 2015 (189)	RCT	Enrolled immediately after birth F/U 7 days	100	Not specified	Tertiary referral hospital	India	Uterine curettage	No intervention	MAP	Length of PN hospital stay Urine output Laboratory values (plt, renal and liver function)

Author and year	Methods		Participants			Intervention			Outcomes	
	Study design	Duration	n ^a	Age /y [†]	Setting	Country	Intervention	Control(s)	Primary	Secondary
ORGANISATION OF CARE (2 studies)										
York 1997 (197)	RCT	Enrolled immediately after birth F/U 8 weeks	96 [§]	28±7 27±7	Tertiary referral	USA	Contact with nurse specialist; early discharge if criteria met; 2 scheduled home visits and 10 telephone calls (twice weekly for 2 weeks, then weekly for 6 weeks) during F/U	Standard care	Postnatal readmission to secondary care	Functional status Patient satisfaction Neonatal rehospitalisation / acute neonatal care Cost
Bibbo 2014 (231)	Retrospective cohort study	F/U not specified (but >7 days)	138	Not specified	Tertiary referral hospital	USA	Specialised postpartum clinic	Usual care	Postnatal readmission to secondary care and triage visits	Primary care provider F/U

[§] Mixture of hypertension and diabetes – unable to separate

Table 6: Excluded studies (n=35)

	Population not postnatal	Intervention not targeted at management of BP	No control group	Study design
n	4	6	20	3
Author and year	Berks 2015 (232) Gerard 1983 (233) Scardo 1999 (234) Wacker 2006 (235)	Chandrasekaran 2015 (236) Ehrenberg 2004 (237) Ehrenberg 2006 (238) Ossada 2016 (239) Wasden 2012 (240) Younger-Lewis 2016 (241)	Al Waili 2004 (242) Alicino 1962 (243) Barton 1991 (244) Belfort 1988 (245) Belfort 1992 (246) Bittle 2014 (247) Bosio 2003 (136) Correa 1982 (248) Dulitzky 1987 (249) Hirshberg 2016 (250) Hirshberg 2017 (138) Hunter 1961 (251) Onishi 2015 (252) Robinson 1964 (253) Rodriguez 2012 (254) Saghir 2015 (255) Smith 2014 (256) Sukerman-Voldman 1985 (257) Taslimi 1991 (258) Tkacheva 2006 (259) Wacker 1994 (260) Walters 1984 (261)	Editor, Emergency Medicine 1990 (262) Cursino 2015 (263) Gallegos 1961 (264)

Of the included RCTs, 30/32 (94%) were judged to be at high overall risk of bias by both reviewers, 23 (72%) for multiple domains. Only 2/32 (6%) were thought to be clearly at low risk of bias (Table 7) (200-203). All included cohort studies were deemed to have a high risk of bias in at least one of the three domains specified by the Newcastle Ottawa Scale – selection of participants, comparability of cohorts and outcome assessment (Table 8).

Table 7: Risk of bias in included randomised controlled trials and quasi-randomised studies (n=32)

Author and year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
ANTIHYPERTENSIVE MEDICATIONS							
Fidler 1982(210)	Unclear	Unclear	Unclear	Unclear	High	High	Low
Garden 1982(195)	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Mabie 1987 (193)	Unclear	Unclear	High	High	Low	Low	High
Griffis 1989 (206, 207)	Unclear	Low	High	High	High	High	High
Barton 1990 (203)	Low	Low	Low	Low	Low	Low	Low
Walss Rodriguez 1991 (208)	Low	Low	High	High	Unclear	Unclear	Low
Vermillion 1999 (192)	Low	Low	Low	Low	Low	Low	High
Begum 2002 (188)	High	High	High	High	Unclear	Unclear	High
Sayin 2005 (204)	Unclear	Unclear	High	High	Low	Unclear	High
Hennessy 2007 (194)	Unclear	Low	High	High	Low	Low	High
Vigil-de-Gracia 2007 (209)	Low	Low	High	High	Low	Low	Low
Gaisin 2013 (196)	Unclear	Unclear	High	High	Unclear	High	High
Gaisin 2014 (212)	Unclear	Unclear	High	High	Unclear	Unclear	High
Noronha Neto 2016 (200-202)	Low	Low	Low	Unclear	Low	Low	Low
Sharma 2016 (198, 199)	Low	Low	High	High	Unclear	Low	Low
DIURETICS							
Matthews 1997 (215)	Unclear	Low	Low	Low	Low	Unclear	High
Ascarelli 2005 (187)	Unclear	Low	High	High	Unclear	High	Low
Amorim 2015 (216)	Low	Low	Low	Low	Low	High	Low
Veena 2017 (190)	Low	Low	High	High	Unclear	Unclear	Unclear
OTHER DRUGS							
Weiner 1982 (217)	Unclear	Unclear	Low	Low	Unclear	Unclear	High
Weiner 1984 (218)	Low	Unclear	Low	Low	Low	Unclear	High
Montenegro 1985 (219)	Unclear	Unclear	Low	Low	High	High	High
Barrilleaux 2005 (222, 223)	Low	Low	Low	Low	Low	High	High
Hladunewich 2006 (220)	Low	Low	Low	Low	High	High	High
Liu 2009 (221)	High	High	High	High	High	Unclear	High
UTERINE CURETTAGE							
Magann 1993 (226)	Low	Low	High	High	Unclear	Unclear	Low
Magann 1994 (227)	Low	Unclear	High	High	Unclear	Unclear	Low
Gomez 2005 (229)	Unclear	Unclear	High	High	Unclear	High	Low
Alkan 2006 (230)	Unclear	Unclear	High	High	Low	High	High
Ragab 2013 (186)	Low	Low	High	High	Low	Low	Low
Mallapur 2015 (189)	Low	Unclear	High	High	Unclear	Unclear	High
ORGANISATION OF CARE							
York 1997 (197)	Unclear	Low	High	High	Unclear	Unclear	High

Table 8: Risk of bias in included cohort studies (n=7)

Author and year	Selection				Comparability [*]	Outcome		
	Representative-ness [†]	Selection of non-exposed [‡]	Ascertainment of exposure [§]	Outcome of interest not present at start		Assessment ^{**}	F/U long enough	Adequacy of F/U ^{††}
ANTIHYPERTENSIVE MEDICATIONS								
Krebs 1956(213, 214)	Low (a)	Low (a)	Unclear (d)	Low (Yes)	Low (a)	High (b)	Low (Yes)	Unclear (d)
Palot 1979(205)	Unclear (d)	Low (a)	Unclear (d)	Low (Yes)	High (Neither)	Unclear (d)	Low (Yes)	Unclear (d)
Shumard 2016(211)	Low (a)	Low (a)	Low (a)	Low (Yes)	High (Neither)	Low (a)	Low (Yes)	Low (a)
OTHER DRUGS								
Shigemitsu 2015(224)	Unclear (d)	Unclear (c)	Low (a)	Low (Yes)	High (Neither)	Low (a)	Low (Yes)	Unclear (d)
UTERINE CURETTAGE								
Salvatore 1967(225)	High (b)	High (b)	Low (a)	Low (Yes)	High (Neither)	Low (a)	Low (Yes)	Low (a)
Gocmen 1996(228)	Unclear (d)	Unclear (c)	Unclear (d)	Low (Yes)	High (Neither)	Unclear (d)	High (No)	Unclear (d)
ORGANISATION OF CARE								
Bibbo 2014(231)	Unclear (d)	Unclear (c)	Unclear (d)	Low (Yes)	High (Neither)	Unclear (d)	Low (Yes)	Unclear (d)

2.4.3 Summary of main results

2.4.3.1 How should blood pressure be monitored in women with hypertensive disorders of pregnancy postpartum?

No studies specifically addressed the frequency or method of BP monitoring postpartum. Two evaluated the impact of postpartum care organization (n=234), using postnatal readmission rate as their primary outcome (Table 5). Neither reported maternal mortality or morbidity, nor any measure of BP control (Table 10) (197, 231).

^{*} (a) study controls for most important factor; (b) study controls for any additional factor

[†] (a) truly representative of the average in the community; (b) somewhat representative of the average in the community; (c) selected group of users e.g. nurses, volunteers; (d) no description of the derivation of the cohort

[‡] (a) drawn from the same community as the exposed cohort; (b) drawn from a different source; (c) no description of the derivation of the non-exposed cohort

[§] (a) secure record (e.g. surgical record); (b) structured interview; (c) written self-report; (d) no description

^{**} (a) independent blind assessment; (b) record linkage; (c) self-report; (d) no description

^{††} (a) complete follow-up; (b) subjects lost to follow-up unlikely to introduce bias (>90% follow-up rate); (c) follow up rate <90% and no description of those lost; (d) no statement

One assessed the introduction of a specialized postpartum clinic (no further details given), and demonstrated an increased postnatal readmission and triage visit rate (clinic group 22%, usual care group 9%; difference 13%, $p<0.04$). 86% of readmissions occurred before a participant was seen in the clinic, 67% in the first ten days after childbirth (231). The second study evaluated specialist nurse follow-up, including home visits and telephone contact, and reported no significant difference in the postnatal readmission rate compared to standard care (197). Neither study reported safety data (Table 10).

2.4.3.2 What blood pressure thresholds should be used for antihypertensive treatment initiation, adjustment and cessation postpartum?

No relevant studies were identified.

2.4.3.3 Which antihypertensive medication(s) should be used postpartum?

Fifteen randomised trials (n=645), one quasi-randomised trial (15 participants), and three retrospective cohort studies (n=322) evaluated antihypertensive medications (Table 11). Only two studies reported maternal mortality (204, 209), and two (205, 209) reported maternal morbidity: no differences between groups were reported for either outcome (Table 9). Twelve studies reported safety data in comparisons between multiple classes of antihypertensive agents (Table 9). No clear differences were established, although one study found more minor side effects reported with oral nifedipine than with oral labetalol (198).

The vast majority of included studies evaluated either acute control of severe hypertension (7/18, 39%) or control in the few days after delivery, whilst women remained hospital inpatients (9/18, 50%). Only three studies, two published only as conference abstracts, evaluated BP control in the weeks and months following hospital discharge (196, 198, 199, 212).

2.4.3.3.1 Calcium-channel blockers

Three small studies examined oral nifedipine (n=135): nifedipine resulted in a greater decrease in mean arterial pressure (MAP) 18-24 hours after childbirth than placebo (nifedipine group 93.9±1.6mmHg, placebo group 100.2±2.6mmHg: difference 6.3mmHg, $p<0.05$), but not at other time points to 48 hours (one RCT, n=31) (203). Nifedipine controlled severe hypertension to <160/100mmHg more quickly than labetalol (nifedipine group 25.1±13.6 minutes, labetalol group 43.6±25.4 minutes: difference 18.5 minutes, $p=0.002$; one RCT, n=21) (192). A single RCT (n=83), reported no significant difference in the time taken to control BP to <150/100mmHg when comparing nifedipine with methyldopa (204).

2.4.3.3.2 Vasodilators

Six studies looked at the use of vasodilators (n=252). All utilized hydralazine as either intervention or control, via a range of administration routes: bolus intravenous hydralazine controlled severe hypertension more quickly than continuous infusion (hydralazine bolus group 65.23±23.38 minutes, hydralazine infusion group 186.36±79.77 minutes: difference -121.13 minutes, $p<0.001$); one quasi-randomised study, n=15) (188). Intramuscular hydralazine produced a more significant improvement in MAP at six hours than intravenous methyldopa (hydralazine group 104.5mmHg, methyldopa group 112mmHg: difference -7.5mmHg, $p=0.0057$) but not at other time points to 24 hours (one RCT, n=26) (206, 207). There was no difference in BP control when comparing oral hydralazine with oral nifedipine (one RCT, n=38), or intravenous labetalol (one RCT, n=82) (208, 209).

Bolus diazoxide was significantly more effective in achieving the target BP of ≤140/90mmHg than intravenous hydralazine (diazoxide group 67%, hydralazine group 43%: RR 0.64, 95% confidence interval 0.46-0.89; one RCT, n=37) (194). One retrospective cohort study did not present any statistical analysis (205).

2.4.3.3.3 Beta-blockers

Five studies assessed the efficacy of beta-blockers (four RCTs and one retrospective cohort study, n=305). Two RCTs compared intravenous labetalol with intravenous hydralazine/dihydralazine: one involved only six postnatal women and presented no statistical analysis of the data (195). The other found a significantly greater mean maximal decrease in MAP with intravenous labetalol (labetalol group 25.5 ± 11.2 mmHg, hydralazine group 33.3 ± 13.2 mmHg; difference -7.8 mmHg, $p=0.02$; one RCT, n=32) (193). Results conflicted regarding whether oral labetalol was more or less effective than oral nifedipine: a cohort study reported that labetalol controlled BP less rapidly than nifedipine (labetalol group 2.7 days, nifedipine group 1.7 days: difference 1.0 days, $p=0.0031$; one retrospective cohort study, n=128) (211). However, this result was not replicated by a RCT, where the time to BP control was similar in the two groups (n=50) (198, 199). There was no difference in length of postnatal stay (one RCT (198, 199) and one retrospective cohort study (211); n=178). Timolol was effective in decreasing DBP on day one postnatal when compared with methyldopa (timolol group 88.7 mmHg, methyldopa group 93.8 mmHg; difference -5.1 mmHg, $p<0.05$; one RCT, n=80) (210).

2.4.3.3.4 Other antihypertensive medications

No statistically significant difference was found between oral clonidine and oral captopril in the incidence of episodes of postpartum severe hypertension (one RCT, n=90) (201, 202). Two RCTs evaluating indapamide versus methyldopa found no difference in BP control (n=60) (196, 212). One retrospective cohort study (n=140) compared reserpine with phenobarbital: the results suggested that reserpine may achieve faster and greater BP reduction (data extracted from graphs; no statistical analysis). No adverse events were reported in the intervention group (213, 214).

Table 9: Primary outcome and safety data reporting in included studies (antihypertensive medications, 18 studies)

Author and year	Intervention	Control	Primary outcome assessment*					Safety data reporting	Results (for reported outcomes)	
			Maternal mortality	Maternal morbidity†	SBP control	DBP control	MAP control			
CALCIUM CHANNEL BLOCKERS										
Barton 1990 (203)	Nifedipine (oral)	Placebo			●	●	●		SBP control: no significant difference. DBP control: no significant difference. MAP control: improved in nifedipine group (difference 6.3mmHg, $p<0.05$).	
Vermillion 1999 (192)	Nifedipine (oral)	Labetalol (IV bolus)			●	●		●	SBP control: improved in nifedipine group (difference in time to target BP 18.5 minutes, $p=0.002$). DBP control: improved in nifedipine group (difference in time to target BP 18.5 minutes, $p=0.002$). Safety: no significant difference. 1/25 nifedipine group became hypotensive.	
Sayin 2005 (204)	Nifedipine (oral)	Methyldopa (oral)	●		●	●			Maternal mortality: no significant difference. SBP control: no significant difference. DBP control: no significant difference.	
VASODILATORS										
Palot 1979 (205)	Hydralazine (IV infusion) & furosemide (IV bolus)	Clonidine (IV) & furosemide (IV bolus)		●					Maternal morbidity: no statistical analysis.	
Griffis 1989 (206, 207)	Hydralazine (IM)	Methyldopa (IV bolus)					●	●	MAP control: no significant difference. Safety: no significant difference. No side effects reported in either group.	
Walss Rodriguez 1991 (208)	Hydralazine (oral) & nifedipine (oral, as required)	Nifedipine (oral, as required)			●	●			SBP control: no significant difference. DBP control: no significant difference.	
Begum 2002 (188)	Hydralazine (IV bolus)	Hydralazine (IV infusion)				●		●	DBP control: improved in bolus hydralazine group (difference in time to target DBP 121.1 minutes, $p<0.001$). Safety: no significant difference. No side effects reported in either group.	

Abbreviations: DBP = diastolic blood pressure; IM = intramuscular; IV = intravenous; MAP = mean arterial pressure; NS = non-significant; SBP = systolic blood pressure

* ● = improved in intervention group; ● = no significant difference; ● = improved in control group; ● = unclear

† Ischaemic stroke, intracranial haemorrhage, eclamptic seizure; development of preeclampsia with severe features; postnatal complication requiring intervention

Author and year	Intervention	Control	Primary outcome assessment*					Safety data reporting	Results (for reported outcomes)
			Maternal mortality	Maternal morbidity [†]	SBP control	DBP control	MAP control		
Vigil de Gracia 2007 (209)	Hydralazine (IV bolus)	Labetalol (IV bolus)	●	●	●	●		●	Maternal mortality: no significant difference. Maternal morbidity: no significant difference. SBP control: no significant difference. DBP control: no significant difference. Safety: no significant difference. Small numbers of side effects reported in both groups.
Hennessy 2007 (194)	Diazoxide (IV bolus)	Hydralazine (IV bolus)			●	●			SBP control: improved in diazoxide group (difference in percentage achieving target BP 23%, $p<0.01$). DBP control: improved in diazoxide group (difference in percentage achieving target BP 23%, $p<0.01$).
BETA BLOCKERS									
Garden 1982 (195)	Labetalol (IV infusion)	Dihydralazine (IV infusion)				●		●	DBP control: no statistical analysis. Safety: no statistical analysis. 1/6 labetalol group developed bronchospasm. 4/6 dihydralazine group developed tachycardia and 1/6 developed oliguria. 4/6 dihydralazine group drug stopped due to a precipitous fall of DBP to 40-50mmHg.
Fidler 1982 (210)	Timolol (oral)	Methyldopa (oral)			●	●		●	SBP control: improved in timolol group (difference 5.1mmHg, $p<0.05$). DBP control: no significant difference. Safety: no statistical analysis. 1/40 timolol group became disorientated. 1/40 methyldopa group became hypotensive and 1/40 became drowsy.
Mabie 1987 (193)	Labetalol (IV bolus)	Hydralazine (IV bolus)					●	●	MAP control: improved in hydralazine group (difference 7.8mmHg ($p=0.02$)). Safety: no statistical analysis. 1/40 labetalol group developed scalp-tingling. 2/20 hydralazine group developed headaches.
Sharma 2016 (198)	Labetalol (oral)	Nifedipine (oral)			●	●		●	SBP: no significant difference. DBP: no significant difference. Safety: No major side effects reported in either group. Minor side effects more commonly reported in nifedipine group (20% labetalol, 48% nifedipine, $p=0.04$).
Shumard 2016 (211)	Labetalol (oral)	Nifedipine (oral)			●	●			SBP control: improved in nifedipine group (difference in time to achieve target BP 1 day, $p=0.0031$). DBP control: improved in nifedipine group (difference in time to achieve target BP 1 day, $p=0.0031$).
OTHER									
Gaisin 2013 (196)	Indapamide (oral)	Methyldopa (oral)			●	●		●	SBP control: no significant difference. DBP control: no significant difference. Safety: no statistical analysis, no details reported.

Author and year	Intervention	Control	Primary outcome assessment*					Safety data reporting	Results (for reported outcomes)
			Maternal mortality	Maternal morbidity [†]	SBP control	DBP control	MAP control		
Gaisin 2014 (212)	Indapamide (oral) & ursodeoxycholic acid (oral)	Methyldopa (oral)			●	●		●	SBP control: no significant difference. DBP control: no significant difference. Safety: no significant difference. No adverse events reported in either group.
Krebs 1956 (213, 214)	Reserpine (oral or IM)	Phenobarbital			●	●		●	SBP control: no statistical analysis. DBP control: no statistical analysis. Safety: no statistical analysis. No adverse events reported in reserpine group, no comment on control.
Katz 2015 (201, 202)	Clonidine (oral)	Captopril (oral)			●	●		●	SBP control: improved in clonidine group (difference in number of episodes of high BP 1.4, $p<0.08$). DBP: improved in clonidine group (difference in number of episodes of high BP 1.4, $p<0.08$). Safety: no significant difference. Adverse reactions 18.6% clonidine, 28.8% captopril, $p=NS$.

2.4.3.4 What are the benefits and harms of other therapeutic interventions for women with hypertensive disorders of pregnancy postpartum?

2.4.3.4.1 Loop Diuretics

Four RCTs (n=503) examined loop diuretics compared to placebo in hypertension management postpartum in women with HDP. None reported maternal mortality or safety data, and two reported major maternal morbidity, neither demonstrating a difference between groups (Table 10) (187, 190).

One RCT (n=120) reported significant improvement in the primary outcome of mean SBP and DBP with oral furosemide versus placebo (magnitude of difference or time points of measurements not stated, $p<0.001$) (216). This was not the case in the other placebo-controlled randomised trial, which found no significant difference (n=19) (215). Two further RCTs (n=364) found no significant difference in BP control with oral furosemide versus usual care (187, 190). In one of these, subgroup analysis of women with severe preeclampsia (n=70) found women who received oral furosemide had a significantly lower SBP day 2 postpartum (furosemide group 142 ± 13 mmHg, usual care group 153 ± 19 mmHg; difference -11mmHg, $p<0.004$), but not at other time points (187). In the other trial (n=100), furosemide appeared to reduce the need for additional antihypertensive treatment during the three days of therapy (furosemide group 8.0%, usual care group 26.0% difference 18%, $p=0.017$), but this did not persist to hospital discharge (190).

2.4.3.4.2 Other drugs

Five RCTs, one quasi-randomised study and one retrospective cohort study investigated the utility of different drug classes in HDP postpartum (Table 5). Three studies reported safety data, but only one study reported maternal mortality, demonstrating no difference between groups (224), and none reported major maternal morbidity (Table 10).

Three small, crossover RCTs, conducted in the 1980s, examined the use of selective serotonin re-uptake inhibitors (SSRIs) compared with placebo (n=55). All studies showed a significant reduction in BP with SSRIs compared to placebo (range 25.6-34mmHg) (217-219). These data suggest efficacy for

this drug class in hypertension management, but do not provide any information regarding relative effectiveness compared to standard antihypertensive drugs. Only one reported safety data: although no statistical analysis was performed there were a number of side effects reported in the SSRI group (218).

Two studies evaluated alternative therapies (n=117): there was no difference in BP control with L-arginine supplementation compared with placebo (one RCT, n=45). In this study, no adverse effects were reported from the intervention (220). One reported accelerated recovery of albuminuria with administration of shengkangbao (Chinese herbal medicine) versus placebo (one quasi-randomised study, n=72). However, the clinical relevance of this outcome is uncertain, there were no differences between groups in the secondary outcomes of SBP, DBP or serum creatinine and no safety data were reported (221).

A single RCT assessed corticosteroids in the management of severe pre-eclampsia and eclampsia postpartum (n=157) (222, 223). No difference was demonstrated between groups in the primary outcome of antihypertensive medication requirement or in the secondary outcomes of MAP or need for critical care admission, and no safety data were reported. There were small, statistically significant differences found in some laboratory values (platelet count, lactate dehydrogenase and aspartate transaminase). However, the authors acknowledged that the absolute differences were too small to be clinically relevant (222).

A very small retrospective cohort study suggested an improvement in MAP with the addition of carperitide (atrial natriuretic peptide) to standard therapy (n=16), and no adverse effects related to the intervention were reported (224). However, the magnitude of the difference was not published, and the study was too small to draw any firm conclusions.

2.4.3.4.3 Uterine curettage

This review was not limited to pharmaceutical interventions, so this section discusses the evidence regarding a surgical procedure to ameliorate HDP. Six RCTs and two prospective cohort studies (n=837) have explored the role of uterine curettage in postpartum hypertension management. Uterine curettage is a similar process to that used in the surgical management of miscarriage: the lining of the uterus is scraped after completion of the third stage of labour in order to maximize placental tissue removal. This may be under direct vision following caesarean section, or via the transcervical route following vaginal birth. The latter approach may be ultrasound-guided, and necessitates some additional form of anaesthesia. The theory underlying this intervention is that gestational hypertension and preeclampsia are placenta-mediated, and therefore ensuring complete evacuation of the uterus following childbirth may accelerate recovery (251, 265).

Seven studies explicitly stated they included both participants who delivered vaginally and those delivered by caesarean: four reported numbers undergoing vaginal delivery (n=248) and caesarean (n=321). One made no comment about mode of birth (228). Only one study reported maternal mortality: no difference found between groups (186). Two reported major maternal morbidity. Neither performed any statistical analysis (Table 10), however, both studies did suggest a reduction in the absolute number of eclamptic seizures in the curettage group compared to no intervention (186, 225). In one, however, there was a potentially important difference between the study groups: 28/28 (100%) in the control group were eclamptic at enrolment, compared to 9/20 (45%) in the intervention group (225). Four studies reported safety data, with none reporting any complications related to the intervention (Table 10) (226, 227, 229, 230).

All eight studies compared curettage with standard care (i.e. no additional intervention), and all suggested that uterine curettage resulted in a significantly lower BP (186, 189, 225-230). One of these had two control groups: standard care and oral nifedipine: when compared to oral nifedipine, no difference was noted with curettage (227).

Five studies reported the magnitude of the difference in MAP between curettage and usual care: range 6-13mmHg (186, 189, 226, 227, 230). Only two of these reported BP data beyond 24 hours postpartum. One RCT reported a significantly lower MAP at 48 hours with curettage (curettage group 104mmHg, usual care group 113mmHg: difference 9mmHg, $p=0.0017$; $n=45$) (227), but the other RCT demonstrated no significant difference in MAP at 48 hours ($n=420$) (186).

One study demonstrated that a greater proportion of the intervention group attained the target BP of <140/90mmHg at 24 hours (curettage group 9/20 (45%), usual care group 3/28 (11%): difference 34%, no p value quoted) and 48 hours postpartum (curettage group 14/20 (70%), usual care group 8/28 (29%): difference 41%, no p value quoted) (225). Two studies did not present the size of the difference between groups (228, 229).

Table 10: Primary outcome and safety data reporting in included studies (loop diuretics, other drugs, uterine curettage and organisation of care, 22 studies)

Author and year	Intervention	Control	Primary outcome assessment [†]					Safety data reporting	Results (for reported outcomes)	
			Maternal mortality	Maternal morbidity [†]	SBP control	DBP control	MAP control			
LOOP DIURETICS (3 studies)										
Matthews 1997 (215)	Furosemide (oral)	Placebo						●		MAP control: no significant difference.
Ascarelli 2005 (187)	Furosemide (oral)	No intervention		●	●	●				Maternal morbidity: no significant difference. SBP control: no significant difference. DBP control: no significant difference.
Amorim 2015 (216)	Furosemide (oral)	Placebo			●	●	●			SBP control: improved in furosemide group (difference not stated, <i>p</i> <0.001). DBP control: improved in furosemide group (difference not stated, <i>p</i> <0.001). MAP control: improved in furosemide group (difference not stated, <i>p</i> <0.001).
Veena 2017 (190)	Furosemide (oral) + nifedipine (oral)	Nifedipine (oral)		●	●	●	●			Maternal morbidity: no significant difference. SBP control: no significant difference. DBP control: no significant difference. MAP control: no significant difference.
OTHER DRUGS (7 studies)										
Selective 5-HT antagonists										
Weiner 1982 (217)	R41468 (IV infusion)	Placebo						●		MAP control: improved in SSRI group (difference 25.6mmHg, <i>p</i> <0.001).
Weiner 1984 (218)	Ketanserin (IV infusion)	Placebo			●	●	●	●	●	SBP control: improved in SSRI group (difference in SBP decline 34mmHg, <i>p</i> <0.001). DBP control: improved in SSRI group (difference in DBP decline 27mmHg, <i>p</i> <0.001). MAP control: improved in SSRI group (difference not stated, <i>p</i> <0.001) Safety: no statistical analysis. 3/20 SSRI group experienced blurred vision: 1 of these was hypotensive (responded to hydration). 1/20 SSRI group experienced mild euphoria.

Abbreviations: DBP = diastolic blood pressure; 5-HT = 5-hydroxytryptamine; IM = intramuscular; IV = intravenous; MAP = mean arterial pressure; SBP = systolic blood pressure

^{*} ● = improved in intervention group; ● = no significant difference; ● = improved in control group; ● = unclear

[†] Development of pre-eclampsia with severe features (section 1.3)

Author and year	Intervention	Control	Primary outcome assessment*					Safety data reporting	Results (for reported outcomes)
			Maternal mortality	Maternal morbidity [†]	SBP control	DBP control	MAP control		
Montenegro 1985 (219)	Ketanserin (IV bolus +/- infusion)	Placebo			●	●	●		SBP control: improved in SSRI group (absolute difference not stated, $p<0.001$). DBP control: improved in SSRI group (absolute difference not stated, $p<0.001$). MAP control: improved in SSRI group (absolute difference not stated, $p<0.001$).
Alternative therapies									
Hladunewich 2006 (220)	L-arginine (oral or IV bolus)	Placebo			●	●	●	●	SBP control: no significant difference. DBP control: no significant difference. MAP control: no significant difference. Safety: no significant difference. No adverse events reported in either group.
Liu 2009 (221)	Shengkangbao (oral or IV bolus)	No intervention			●	●			SBP control: no significant difference. DBP control: no significant difference.
Steroids									
Barrilleaux 2005 (222, 223)	Dexamethasone (IV bolus)	Placebo					●		MAP control: no significant difference.
Atrial natriuretic peptide									
Shigemitsu 2015 (224)	Carperitide (route not specified)	No intervention	●				●	●	Maternal mortality: no significant difference. MAP control: no significant difference. Safety: no significant difference. No adverse events reported in either group.
UTERINE CURETTAGE (8 studies)									
Salvatore 1967 (225)	Uterine curettage	No intervention		●	●	●			Maternal morbidity: no statistical analysis. SBP control: no statistical analysis. DBP control: no statistical analysis.
Magann 1993 (226)	Uterine curettage	No intervention					●	●	MAP control: improved in curettage group (difference at different time points to 24h postpartum 6-10mmHg, $p<0.05$). Safety: no significant difference. No complications reported from curettage (follow-up to 7 weeks postpartum).
Magann 1994 (227)	Uterine curettage	Nifedipine (oral) or no intervention					● ●	●	MAP control: no significant difference between curettage and oral nifedipine; improved in curettage group compared to usual care (difference at 8-48h postpartum 9-13mmHg, $p=0.0017$). Safety: no significant difference. No complications/side effects reported from curettage or nifedipine (follow-up to 7 weeks postpartum).
Gocmen 1996 (228)	Uterine curettage	No intervention					●		MAP control: improved in curettage group (difference not stated, $p=0.01$).

Author and year	Intervention	Control	Primary outcome assessment*					Safety data reporting	Results (for reported outcomes)
			Maternal mortality	Maternal morbidity [†]	SBP control	DBP control	MAP control		
Gomez 2005 (229)	Uterine curettage	No intervention					●	●	MAP control: improved in curettage group (difference not stated, $p<0.001$). Safety: no significant difference. No complications reported from curettage.
Alkan 2006 (230)	Uterine curettage	No intervention					●	●	MAP control: improved in curettage group (difference 6.8mmHg, $p<0.05$). Safety: No significant difference. No complications reported from curettage.
Ragab 2013 (186)	Uterine curettage	No intervention	●	●			●		Maternal mortality: no significant difference. Maternal morbidity: no statistical analysis. MAP control: improved in curettage group (difference at 6h postpartum 12.3mmHg, $p=0.02$, difference at 24h postpartum 9.2mmHg, $p=0.01$)
Mallapur 2015 (189)	Uterine curettage	No intervention					●		MAP control: improved in curettage group (difference at 4h postpartum 7.6mmHg, $p<0.001$).
ORGANISATION OF CARE (2 studies)									
York 1997 (197)	Nurse specialist follow-up	No intervention							N/A
Bibbo 2014 (231)	Specialist postpartum clinic	No intervention							N/A

Table 11: Main results (39 studies)[‡]

ANTIHYPERTENSIVE MEDICATIONS (18 studies)			
Calcium channel blockers			
BARTON 1990 (203)			
Population: Postnatal women with severe pre-eclampsia			
Setting: Tertiary referral centres, USA			
Intervention: Nifedipine 10mg PO 4-hourly for 48 hours			
Comparison: Placebo			
Primary outcome MAP (18-24 hours after birth)	Treatment effect Nifedipine group 93.9±1.6mmHg, placebo group 100.2±2.6mmHg. Difference -6.3mmHg ($p<0.05$).	Number of participants 31 (16 intervention, 15 control); follow-up complete for all participants	Quality of the evidence Double-blind RCT; overall low risk of bias
VERMILLION 1999 (192)			
Population: Antenatal and postnatal women with severe pre-eclampsia or super-imposed pre-eclampsia			
Setting: Tertiary referral centres (USA)			
Intervention: Nifedipine 10mg stat PO then 20mg every 20 minutes until BP <160/110mmHg or max 5 doses (90mg) + IV placebo			
Comparison: Labetalol 20mg, then 40mg, then 80mg IV every 20 minutes until BP <160/110mmHg or max 5 doses (300mg) + PO placebo			
Primary outcome SBP + DBP (time to target <160/100mmHg)	Treatment effect Nifedipine group 25.1±13.6 minutes, labetalol group 43.6±25.4 minutes. Difference -18.5 minutes ($p=0.002$).	Number of participants 50 (21 postnatal: 10 intervention, 11 control); follow-up complete for all participants	Quality of the evidence Double-blind RCT; overall high risk of bias (other bias); small number of postnatal women (42%) ($n<30$): unable to obtain data for postnatal subgroup
SAYIN 2005 (204)			
Population: Postnatal women with pre-eclampsia, severe pre-eclampsia, superimposed pre-eclampsia or eclampsia			
Setting: Tertiary referral centres (Turkey)			
Intervention: Nifedipine 10mg PO 6-hourly until BP <150/100mmHg for 48 hours			
Comparison: Methyldopa 250mg PO 8-hourly			
Primary outcome SBP + DBP (time to target <150/100mmHg)	Treatment effect Nifedipine group 6.7±2.5 days; methyldopa group 8.6±5.5 days. Difference -1.9 days (NS).	Number of participants 83 (42 intervention, 41 control); follow-up complete for all participants	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains)
Vasodilators			
PALOT 1979 (205)			
Population: Postnatal women with 'arterial hypertension of labour and the postpartum period'			
Setting: Not specified (France)			
Intervention: Hydralazine 5mg IV stat then 1% IV infusion, furosemide 20mg IV stat and 30% hypertonic glucose			
Comparison: Clonidine IV and furosemide 20mg IV stat			

[‡] **Abbreviations:** DBP = diastolic blood pressure; IM = intramuscular; IV = intravenous; MAP = mean arterial pressure; NS = non-significant; PO = oral; RCT = randomised controlled trial; SBP = systolic blood pressure

Primary outcome Maternal morbidity (development of pre-eclampsia with severe features)	Treatment effect Hydralazine group: no women developed eclampsia, clonidine group: 2 women developed eclampsia. No statistical analysis.	Number of participants 54 (11 intervention, 24 control, 19 non-systematic treatment); completeness of follow-up not specified	Quality of the evidence Retrospective cohort study; overall high risk of bias (comparability); no statistical analysis
GRIFFIS 1989 (206, 207) Population: Postnatal women with pre-eclampsia Setting: Tertiary referral centres (USA) Intervention: Hydralazine 20mg IM 6-hourly for 24h Comparison: Methyldopa 250mg IV 6-hourly for 24h			
Primary outcome MAP (mean at 6 and 12 hours)	Treatment effect 6 hours: hydralazine group 104.5mmHg, methyldopa group 112mmHg. Difference -7.5mmHg ($p=0.0057$). 12 hours: hydralazine group 100mmHg, methyldopa group 108mmHg. Difference -8mmHg (NS).	Number of participants 26 (12 intervention, 14 control); follow-up complete for all participants	Quality of the evidence Open-label RC; overall high risk of bias (multiple domains); small sample size ($n<30$)
WALSS RODRIGUEZ 1991 (208) Population: Postnatal women with severe pre-eclampsia Setting: Not specified (Mexico) Intervention: Hydralazine 40mg PO 6-hourly, duration not specified + if DBP >110 mmHg PRN nifedipine 10mg sublingual every 30 minutes, to maximum of 3 doses (30mg) Comparison: Nifedipine 10mg sublingual every 30 minutes if DBP ≥ 110 mmHg			
Primary outcome SBP (mean)	Treatment effect Hydralazine group 143.6mmHg, nifedipine group 138.0mmHg. Difference 5.6mmHg (NS).	Number of participants 38 (18 intervention, 20 control); completeness of follow-up not specified	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains)
BEGUM 2002 (188) Population: Antenatal and postnatal women with eclampsia Setting: Tertiary referral centres (Bangladesh) Intervention: Hydralazine 5mg then 2mg IV bolus every 15 minutes until DBP 90-95mmHg Comparison: Hydralazine 20mg /200ml normal saline IV infusion; 10 drops per min, increased by 5 drops at 15 min intervals; until DBP 90-95mmHg			
Primary outcome DBP (time to target 90-95mmHg)	Treatment effect Bolus hydralazine group 65.23 $\pm$ 23.38 minutes, hydralazine infusion group 186.36 $\pm$ 79.77 minutes. Difference -121.13 minutes ($p<0.001$).	Number of participants 77 (15 postnatal: 9 intervention, 6 control); completeness of follow-up not specified	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains); small number of postnatal women (19%) ($n<30$); unable to obtain data for postnatal subgroup
VIGIL DE GRACIA 2007 (209) Population: Postnatal women with severe gestational hypertension, severe pre-eclampsia or super-imposed pre-eclampsia Setting: Tertiary referral centres (Panama) Intervention: Hydralazine 5mg IV every 20 minutes until BP $<160/110$ mmHg or maximum 5 doses Comparison: Labetalol 20mg, then 40mg, then 80mg IV every 20 minutes until BP $<160/110$ mmHg or maximum 5 doses (300mg)			
Primary outcome SBP + DBP (persistent hypertension $\geq 160/110$ mmHg after 5 doses of medication)	Treatment effect Hydralazine group 0/42, labetalol group 1/40 (NS).	Number of participants 82 (42 intervention, 40 control); follow-up complete for all participants	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains)

HENNESSY 2007 (194)			
Population: Antenatal and postnatal women with pre-eclampsia, superimposed pre-eclampsia or essential hypertension			
Setting: Tertiary referral (Australia)			
Intervention: Diazoxide 15mg IV every 3 minutes, until target BP (140/90mmHg) reached or maximum cumulative dose 300mg			
Comparison: Hydralazine 5mg IV every 20 minutes, until target BP (140/90mmHg) reached or maximum cumulative dose 15mg			
Primary outcome SBP + DBP (proportion achieving target BP ≤140/90mmHg)	Treatment effect Diazoxide group 67%, hydralazine group 43% ($p<0.01$). RR 0.637 (95% CI 0.46 to 0.89) for not reaching target BP with intervention.	Number of participants 124 total (37 postnatal: 11 intervention, 16 control); follow-up complete for all participants	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains); small proportion of postnatal women (30%); unable to obtain data for postnatal subgroup
Beta-blockers			
GARDEN 1982 (195)			
Population: Antenatal and postnatal women with severe pre-eclampsia or eclampsia			
Setting: Tertiary referral (South Africa)			
Intervention: Labetalol 200mg/200ml 5% dextrose, 20mg/h IV infusion, doubled every 30 minutes until DBP <100mmHg or maximum dose 160mg/hour			
Comparison: Dihydralazine 100mg/200ml 5% dextrose, 10mg/h IV infusion, doubled every 30 minutes until DBP <100mmHg or maximum dose 80mg/hour			
Primary outcome DBP (proportion achieving target DBP 90-100mmHg within 2 hours)	Treatment effect Labetalol group 5/6, dihydralazine group 2/6. No statistical analysis.	Number of participants 12 total (6 postnatal: 3 intervention, 3 control); follow-up complete for all participants	Quality of the evidence RCT (blinding not specified); overall high risk of bias (other bias); very small sample size ($n<15$); unable to obtain data for postnatal subgroup
FIDLER 1982 (210)			
Population: Postnatal women with gestational hypertension			
Setting: Tertiary referral (UK)			
Intervention: Timolol 5mg PO 8-hourly for 9 days			
Comparison: Methyldopa 250mg PO 8-hourly for 9 days			
Primary outcome DBP (day 1)	Treatment effect Timolol group 88.7mmHg, methyldopa group 93.8mmHg. Difference - 5.1mmHg ($p<0.05$).	Number of participants 80 (40 intervention, 40 control); follow-up complete in 79/80 (99%)	Quality of the evidence RCT (blinding not specified); overall high risk of bias (multiple domains)
MABIE 1987 (193)			
Population: Antenatal and postnatal women with pre-eclampsia, superimposed pre-eclampsia, eclampsia or essential hypertension			
Setting: Tertiary referral (USA)			
Intervention: Labetalol 20mg IV every 10 minutes then escalating until DBP <100mmHg or maximum cumulative dose reached (300mg)			
Comparison: Hydralazine 5mg IV every 10 minutes until DBP <100mmHg			
Primary outcome MAP (mean maximal decrease)	Treatment effect Labetalol group 25.5±11.2mmHg, hydralazine group 33.3±13.2mmHg. Difference -7.8mmHg ($p=0.02$).	Number of participants 60 (41 postnatal: 27 intervention, 14 control); follow-up complete for all participants	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains)
SHARMA 2017 (198, 199)			
Population: Postnatal women with gestational hypertension or pre-eclampsia			
Setting: Tertiary referral (USA)			
Intervention: Labetalol 200mg PO 12-hourly			
Comparison: Nifedipine XL 30mg PO once daily			

Primary outcome SBP + DBP (time to sustained BP control: absence of severe hypertension for ≥ 12 hours)	Treatment effect Labetalol group 37.6 hours, nifedipine group 38.2 hours. Difference -0.6 hours (NS).	Number of participants 50 (25 intervention, 25 control); follow-up complete for all participants	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains)
SHUMARD 2016 (211) Population: Postnatal women with gestational hypertension or pre-eclampsia Setting: Not specified (USA) Intervention: Labetalol PO (variable dose and frequency) Comparison: Nifedipine PO (variable dose and frequency)			
Primary outcome Length of hospital stay after delivery	Treatment effect Labetalol group 3.5 days, nifedipine group 3.6 days. Difference -0.1 days (NS).	Number of participants 128 (42 intervention, 86 control); follow-up complete for all participants	Quality of the evidence Retrospective cohort study; overall high risk of bias (comparability); conference abstract only, authors did not provide further data
Other antihypertensive medications			
GAISIN 2013 (196) Population: Postnatal women with pre-eclampsia, super-imposed pre-eclampsia or essential hypertension Setting: Not specified (Russia) Intervention: Indapamide 1.5mg PO OD, duration unclear Comparison: Adjusted dose methylodopa			
Primary outcome SBP + DBP	Treatment effect Indapamide group $113 \pm 6 / 74 \pm 4$ mmHg, methylodopa group $116 \pm 5 / 75 \pm 4$ mmHg. Difference -3/+1 mmHg (NS).	Number of participants 30 (15 intervention, 15 control); completeness of follow-up not specified	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains); conference abstract only, authors did not provide further data
GAISIN 2014 (212) Population: Postnatal women with pre-eclampsia Setting: Not specified (Russia) Intervention: Indapamide 1.5mg PO once daily + ursodeoxycholic acid 250mg PO three times daily, duration unclear Comparison: Adjusted dose methylodopa			
Primary outcome SBP + DBP	Treatment effect Indapamide group $122 \pm 6 / 75 \pm 4$ mmHg, methylodopa group $126 \pm 6 / 78 \pm 5$ mmHg. Difference -4/-3 mmHg (NS).	Number of participants 30 (allocation not described); completeness of follow-up not specified	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains); conference abstract only, authors did not provide further data; number of participants in each group not stated
KREBS 1956 (213, 214) Population: Postnatal women with gestational hypertension, pre-eclampsia, severe pre-eclampsia or eclampsia Setting: Not specified (Germany) Intervention: Reserpine 0.25mg PO or intramuscular 6-8 hourly for 7 days Comparison: Phenobarbital			
Primary outcome SBP + DBP (maximal reduction)	Treatment effect Reserpine halved time to maximal BP reduction (no further details reported). No statistical analysis.	Number of participants 140 (70 intervention, 70 control); completeness of follow-up not specified	Quality of the evidence Retrospective cohort study; overall high risk of bias (selection and outcome assessment); no statistical analysis

NORONHA NETO 2016 (200-202)			
Population: Postnatal women with severe HDP			
Setting: Tertiary referral (Brazil)			
Intervention: Clonidine 0.1mg PO repeated every 20 minutes to max 6 doses			
Comparison: Captopril 25mg PO repeated every 20 minutes to max 6 doses			
Primary outcome SBP + DBP (episodes SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg)	Treatment effect Clonidine group 2.1 ± 2.1 episodes, captopril group 3.5 ± 4.7 episodes. Difference -1.4 episodes (NS).	Number of participants 90 (45 intervention, 45 control); completeness of follow-up not specified	Quality of the evidence Double-blind RCT; overall low risk of bias
DIURETICS (4 studies)			
MATTHEWS 1997 (215)			
Population: Postnatal women with severe pre-eclampsia or eclampsia			
Setting: Tertiary referral centres (UK)			
Intervention: Furosemide 40mg PO once daily for 7 days			
Comparison: Placebo			
Primary outcome MAP (decrease)	Treatment effect Intervention group -10.6mmHg, control group -9.75mmHg. Difference -0.85mmHg (NS).	Number of participants 19 (10 intervention, 9 control); follow-up complete in 18/19 (95%)	Quality of the evidence Double-blind RCT; overall high risk of bias (other bias); small sample size ($n < 30$)
ASCARELLI 2005 (187)			
Population: Postnatal women with pre-eclampsia, severe pre-eclampsia or superimposed pre-eclampsia			
Setting: Tertiary referral centres (USA)			
Intervention: Furosemide 20mg PO once daily + potassium 20mEq PO once daily for 5 days			
Comparison: No intervention			
Primary outcome SBP	Treatment effect No significant difference between groups (details not reported). Severe pre-eclampsia ($n=70$) day 2 SBP furosemide group 142 ± 13 mmHg, usual care group 153 ± 19 mmHg. Difference -11mmHg ($p < 0.004$).	Number of participants 264 (132 intervention, 132 control); completeness of follow-up not specified.	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains)
AMORIM 2015 (216)			
Population: Postnatal women with severe pre-eclampsia			
Setting: Tertiary referral (Brazil)			
Intervention: Furosemide 40mg PO once daily for maximum 5 days			
Comparison: Placebo			
Primary outcome SBP + DBP	Treatment effect Furosemide group had significantly improved SBP + DBP. Magnitude of difference not reported ($p < 0.001$).	Number of participants 120 (allocation not described); follow-up complete in 118/120 (98%).	Quality of the evidence Double-blind RCT; overall high risk of bias (reporting bias); conference abstract only, authors did not provide further data; number of participants in each group not stated
VEENA 2017 (190)			
Population: Postnatal women with severe pre-eclampsia			
Setting: Tertiary referral centre (India)			
Intervention: Furosemide 10mg PO once daily plus nifedipine 10mg PO three times daily for 3 days			
Comparison: Nifedipine 10mg PO three times daily for 3 days			

Primary outcome SBP + DBP	Treatment effect No significant difference between groups (absolute values and differences not reported, $p=0.457$ for SBP and $p=0.642$ for DBP).	Number of participants 100 (50 intervention, 50 control); follow-up complete in 98/100 (98%)	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains)
OTHER DRUGS (7 studies)			
Selective 5-HT antagonists			
WEINER 1982 (217) Population: Postnatal women with severe pre-eclampsia Setting: Tertiary referral (USA) Intervention: R41468 IV (dose not specified) bolus then infusion for 90 minutes Comparison: Placebo			
Primary outcome MAP (mean maximal decline)	Treatment effect SSRI group -31.6mmHg, placebo group -6.0mmHg. Difference -25.6mmHg ($p<0.001$).	Number of participants 5 (crossover); follow-up complete in all participants	Quality of the evidence Double blind RCT (crossover); overall high risk of bias (other bias); conference abstract only, authors did not provide further data; very small sample size ($n<15$)
WEINER 1984 (218) Population: Postnatal women with pre-eclampsia and super-imposed pre-eclampsia Setting: Tertiary referral (USA) Intervention: Ketanserin 10mg IV bolus then 4mg/hr IV infusion. Repeat bolus after 5 minutes if no response. Comparison: Placebo			
Primary outcome SBP + DBP (mean maximal decline)	Treatment effect SSRI group -41/-34mmHg, placebo group -7/-7mmHg. Difference -34/-27mmHg ($p<0.001$).	Number of participants 20 (crossover); follow-up complete in all participants	Quality of the evidence Double blind RCT (crossover); overall high risk of bias (other bias); small sample size ($n<30$)
MONTENEGRO 1985 (219) Population: Postnatal women with pre-eclampsia Setting: Tertiary referral (USA) Intervention: Ketanserin 10mg IV bolus, repeated if no response. If no response to second bolus IV infusion 4mg/hr (increments of 2mg/hr every 10 minutes to max 12mg/hr). Comparison: Placebo			
Primary outcome MAP	Treatment effect SSRI group had significantly improved MAP, over 30 minutes after drug administered. $F = 9.66$ ($p<0.01$)	Number of participants 30 (crossover); follow-up complete in 23/30 (77%)	Quality of the evidence Double blind RCT (crossover); overall high risk of bias (multiple domains)
Alternative therapies			
HLADUNEWICH 2006 (220) Population: Postnatal women with pre-eclampsia Setting: Tertiary referral (USA) Intervention: L-arginine 3.5g PO four times daily OR L-arginine 10g IV three times daily (if unable to take PO) for 3-9 days postpartum Comparison: Placebo			
Primary outcome MAP	Treatment effect Day 3: L-arginine group 102 ± 12 mmHg, placebo group 103 ± 12 mmHg. Difference -1mmHg (NS). Day 10: L-arginine group 98 ± 14 mmHg, placebo group 96 ± 1 mmHg. Difference 2mmHg (NS).	Number of participants 45 (22 intervention, 23 control); follow-up complete in 39/45 (87%)	Quality of the evidence Double blind RCT; overall high risk of bias (multiple domains)

LIU 2009 (221)			
Population: Postnatal women with severe pre-eclampsia			
Setting: District general (China)			
Intervention: Shengkangbao 10g PO or IV twice daily for 3 weeks			
Comparison: No intervention			
Primary outcome	Treatment effect	Number of participants	Quality of the evidence
Percentage of cases with positive albuminuria	3 weeks: shengkangbao group 0.7+/-0.8% positive albuminuria, usual care group 1.5+/-0.9%. Difference -0.8% ($p<0.01$).	77 (allocation not described); follow-up complete in 72/77 (94%)	Open-label quasi-randomised study; overall high risk of bias (multiple domains)
Steroids			
BARRILLEAUX 2005 (222, 223)			
Population: Postnatal women with severe pre-eclampsia and eclampsia			
Setting: Tertiary referral (USA)			
Intervention: Dexamethasone 10mg x2, then 5mg x 2 IV 12-hourly for 48 hours			
Comparison: Placebo (IV saline)			
Primary outcome	Treatment effect	Number of participants	Quality of the evidence
Antihypertensive medication requirement	Dexamethasone group 38/77 (49%), placebo group 31/80 (39%) required antihypertensive treatment in the first 48h PN. Difference 10% (NS).	157 (77 intervention, 80 control); follow-up complete in 155/157 (99%)	Double blind RCT; overall high risk of bias (reporting bias)
Atrial natriuretic peptide			
SHIGEMITSU 2015 (224)			
Population: Postnatal women with severe pre-eclampsia, HELLP syndrome or placental abruption			
Setting: Tertiary referral (Japan)			
Intervention: Carperitide (no further details supplied)			
Comparison: No intervention			
Primary outcome	Treatment effect	Number of participants	Quality of the evidence
MAP	Carperitide group had significantly improved MAP at 48 hours. Magnitude of difference not reported, no p value presented.	16 (6 intervention, 10 control); follow-up complete for all participants	Retrospective cohort study; overall high risk of bias (comparability); conference abstract only, authors did not provide further data; small sample size ($n<30$)
UTERINE CURETTAGE (8 studies)			
SALVATORE 1967 (225)			
Population: Postnatal women with severe pre-eclampsia or eclampsia			
Setting: Tertiary referral (Brazil)			
Intervention: Uterine curettage			
Comparison: No intervention			
Primary outcome	Treatment effect	Number of participants	Quality of the evidence
SBP + DBP (proportion achieving target $<140/90$ mmHg)	24 hours: curettage group 45%, usual care group 11%. No statistical analysis. 48 hours: curettage group 70%, usual care group 29%. No statistical analysis.	48 (20 intervention, 28 control); follow-up complete for all participants	Prospective cohort study; overall high risk of bias (comparability); significant differences in study groups (9/20 intervention group eclamptic at enrolment, 28/28 control group)
MAGANN 1993 (226)			
Population: Postnatal women with severe pre-eclampsia			
Setting: Tertiary referral (USA)			
Intervention: Uterine curettage			
Comparison: No intervention			

Primary outcome MAP	Treatment effect Curettage group had significantly improved MAP to 24 hours after birth. Difference -6 to -10mmHg (16 hours $p<0.0002$).	Number of participants 32 (16 intervention, 16 control); completeness of follow-up not specified	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains)
MAGANN 1994 (227) Population: Postnatal women with severe pre-eclampsia Setting: Tertiary referral (USA) Intervention: Uterine curettage Comparison: Oral nifedipine OR no intervention			
Primary outcome MAP	Treatment effect Curettage group had significantly improved MAP 8-48 hours after birth. Difference -9 to -13mmHg ($p=0.0017$). No difference between curettage and nifedipine.	Number of participants 45 (15 intervention, 15 each control group); completeness of follow-up not specified	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains)
GOCMEN 1996 (228) Population: Postnatal women with pre-eclampsia Setting: Tertiary referral (Turkey) Intervention: Uterine curettage Comparison: No intervention			
Primary outcome MAP	Treatment effect Curettage group had significantly improved MAP to 24 hours after birth. Magnitude of difference not reported ($p=0.01$).	Number of participants 50 (30 intervention, 20 control); completeness of follow-up not specified	Quality of the evidence Prospective cohort study; overall high risk of bias (comparability and outcome assessment); conference abstract only, authors did not provide further data
GOMEZ 2005 (229) Population: Postnatal women with severe pre-eclampsia Setting: Tertiary referral (Peru) Intervention: Uterine curettage Comparison: No intervention			
Primary outcome MAP	Treatment effect Intervention group had significantly improved MAP. Time point not specified. Magnitude of difference not reported ($p<0.001$).	Number of participants 86 (27 intervention, 59 control); completeness of follow-up not specified	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains); conference abstract only, authors did not provide further data
ALKAN 2006 (230) Population: Postnatal women with severe pre-eclampsia Setting: Tertiary referral (Turkey) Intervention: Uterine curettage Comparison: No intervention			
Primary outcome MAP	Treatment effect 24 hours: curettage group 103.4 $\pm$ 7.8mmHg, usual care group 110.2 $\pm$ 4.8. Difference -6.8mmHg ($p<0.05$).	Number of participants 56 (31 intervention, 25 control); follow-up complete for all participant	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains)

RAGAB 2013 (186)			
Population: Postnatal women with severe pre-eclampsia or eclampsia Setting: Tertiary referral (Egypt) Intervention: Uterine curettage Comparison: No intervention			
Primary outcome MAP	Treatment effect 6 hours: curettage group 140.1±6.12mmHg, usual care group 152.4±3.7mmHg. Difference -12.3mmHg ($p=0.02$). 24 hours: curettage group 101.4±7.14mmHg, usual care group 110.6±2.22mmHg. Difference -9.2mmHg ($p=0.01$).	Number of participants 420 (220 intervention, 200 control); follow-up complete for all participants	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains)
MALLAPUR 2015 (189)			
Population: Postnatal women with severe pre-eclampsia or eclampsia Setting: Tertiary referral (India) Intervention: Uterine curettage Comparison: No intervention			
Primary outcome MAP	Treatment effect From 4 hours after birth: curettage group 116±4.4mmHg, usual care group 123.6±6.1mmHg. Difference -7.6mmHg ($p<0.001$).	Number of participants 100 (50 intervention, 50 control); completeness of follow-up not specified	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains); conference abstract only, authors did not provide further data
ORGANISATION OF CARE (2 studies)			
YORK 1997 (197)			
Population: Postnatal women with pre-eclampsia or essential hypertension, or diabetes Setting: Tertiary referral (USA) Intervention: Nurse specialist follow-up Comparison: No intervention			
Primary outcome Postnatal readmission to secondary care	Treatment effect No significant difference between groups.	Number of participants 96 (44 intervention, 52 control); completeness of follow-up not specified	Quality of the evidence Open-label RCT; overall high risk of bias (multiple domains); population mixed diabetes and/or hypertension – unable to separate
BIBBO 2014 (231)			
Population: Postnatal women with pre-eclampsia Setting: Tertiary referral (USA) Intervention: Specialised postpartum clinic Comparison: No intervention			
Primary outcome Postnatal readmission to secondary care and triage visits	Treatment effect Clinic group 21.7%, usual care group 8.7%. Difference 13% ($p<0.039$).	Number of participants 138 (69 intervention, 69 control); completeness of follow-up not specified.	Quality of the evidence Retrospective cohort study; overall high risk of bias (comparability); conference abstract only, authors did not provide further data

2.5 Discussion

2.5.1 Main Findings

This review found evidence demonstrating that calcium-channel blockers, vasodilators and beta-blockers lower BP postpartum to a greater or lesser extent (Table 9 and Table 11), but no clear answer to which was most effective and should therefore be preferentially prescribed. All but three included studies examined acute control of severe hypertension or short-term BP control in hospital postpartum (196, 198, 199, 212), and so provide little guidance about prescription in the weeks after discharge. Moreover two of these studies examined thiazide diuretics, not recommended in the UK for use whilst breastfeeding (1). Complete safety data were limited across trials, as were data regarding objective clinical outcomes and two further studies examined drugs not recommended for use postpartum in the UK (methyldopa and reserpine) (103, 266). The trial evaluating captopril used a much higher daily dose than the UK recommended daily starting dose (266), and the Canadian guideline advises that clonidine is known to accumulate in the neonatal serum (9).

Uterine curettage is not currently recommended, due to safety concerns regarding additional anaesthetic and operative risks, and the availability of alternative treatments to lower BP, particularly in the context of vaginal birth (267). However, the included studies consistently demonstrated that curettage improved BP control versus standard care (186, 189, 225-230); with one additionally reporting an equivalent effect to oral nifedipine (227). Amongst the limited presented safety data, no studies reported an excess complication rate (infection or uterine damage) with curettage, but given the low incidence of operative complications, the total population (n=837) was likely insufficient to adequately address potential competing risks. Furthermore, these studies did not demonstrate any impact from curettage on maternal mortality or severe morbidity and concerns exist about some studies' methodology. The evidence reviewed is insufficient to recommend incorporation of this intervention into routine clinical practice.

Four trials evaluating loop diuretics failed to provide conclusive evidence of benefit. Three produced negative results in their main analysis (187, 190, 215), and the single conference abstract which did suggest better BP control with oral furosemide, did not publish the magnitude of the difference, rendering it difficult to assess the clinical relevance (216). In contrast to the Cochrane review (89), this current review concludes, at present, there is no evidence to support the routine use of diuretics postpartum.

No adequate evidence was found to support alternative medications or a particular care model in the management of HDP postpartum. SSRIs substantially reduced BP versus placebo (217-219), but no published data were identified comparing efficacy with standard antihypertensive treatment, so it was difficult to draw meaningful conclusions about clinical application. Neither study evaluating postpartum care organisation reported maternal mortality or morbidity, or any measure of BP control, with both selecting postnatal readmissions as their primary outcome (197, 231). An increased postnatal readmission rate, however, may not necessarily reflect harm: it might instead suggest that a particular model of care can better detect problems in the community and admit appropriately, ultimately resulting in a lower risk to patients.

In light of the heterogeneous nature of research in this field, during the design of this review it was decided to include all interventions targeting hypertension management, but not end-organ complications including eclampsia. Therefore, trials evaluating magnesium sulphate were outside the scope of this review. The relevance of this therapy in women with severe pre-eclampsia, especially in the immediate postnatal period, is not in question: a Cochrane review suggests no uncertainty regarding the effectiveness of this therapy (268).

2.5.2 Strengths and limitations

This systematic review is enhanced by its inclusiveness: RCTs and other experimental study designs (cohort studies, case-control studies and quasi-randomised studies) were eligible. No limitations were imposed in terms of language and publication date, resulting in a comprehensive review that

provides evidence suggesting significant research gaps, consistent with the findings from the Cochrane review (2013) (89). The Cochrane review included only nine trials (author names in bold in Table 5). This review includes an additional 30 studies (19 pre-dating the Cochrane search, and 11 subsequent to it), providing a current and complete summary of all available research in this area.

The applicability of the findings and recommendations from this review are restricted by the low quality of included studies: Both reviewers judged the vast majority to have a high overall risk of bias (Table 7 and Table 8). Nearly one quarter of the included studies (n=9, 23%) were published only as conference abstracts, and therefore not subjected to peer review. Data extraction was restricted to the information provided in the abstracts as no authors provided additional data upon request. These were limiting factors in this analysis, but nonetheless it was felt to be important to include these studies for completeness, especially given the paucity of evidence that exists in this field. A further justification for their inclusion is that half of trials reported in conference abstracts never reach full publication, and positive trials are more likely to be published than negative ones (269), which has the potential to skew the results of a review if they are omitted.

The body of evidence identified was significantly smaller than that underpinning antenatal hypertension management: 18 studies (not restricted to RCTs), involving 982 participants, evaluated antihypertensive drugs postpartum. Furthermore, the size of all but a few individual studies was small: only 8/39 included 100 or more participants, and only 2/39 included 200 or more (186, 187). By comparison, a Cochrane review (2014) evaluated antihypertensive medication for mild to moderate hypertension in pregnancy: 49 RCTs were included (4723 participants) (270). The quantity and quality of evidence supporting the management of HDP is vastly lesser than that available for essential hypertension outside pregnancy, where individual RCTs commonly involve several thousand participants (127).

The majority of identified studies did not report substantive clinical outcomes such as maternal mortality, morbidity or harms (Table 9 and Table 10). Without these, it is difficult to define properly

the potential role of proposed interventions in clinical practice. The incidence of adverse maternal and neonatal outcomes, particularly in high resource settings, is low meaning adequately powering studies for real outcomes of interest is financially demanding. Therefore researchers often employ surrogate outcomes. Additionally, the range of outcomes reported in included studies was broad and inconsistent (Table 5), with BP changes in particular being measured in a variety of different ways, further limiting the comparability of trials. Increasingly, core-outcome sets are being produced, with a view to trials reporting as standard, a minimum set of outcomes that are clinically meaningful and important to patients (271). The hope is that in future this would enhance researchers' ability to synthesize results from different studies to produce high quality evidence. There is consensus about trying to move away from surrogate outcomes, for example time to BP control, as they cannot effectively substitute for clinically important outcomes. An important and clinically meaningful end point should measure how a patient feels, functions, or survives.

2.6 Conclusions

This review has demonstrated a lack of good quality evidence for postpartum hypertension management, emphasizing a need for further RCTs directly comparing different antihypertensive agents, BP thresholds for medication adjustment and different models of care, with outcome measures other than postnatal readmissions. The data regarding uterine curettage justify further research to evaluate clinically meaningful outcomes and procedural risks. It might be pragmatic to confine this to curettage at caesarean section, given concerns regarding surgical intervention after vaginal birth: an additional anaesthetic is not required; infection risk is lowered within a sterile surgical field compared to the transcervical route; and curettage under direct vision limits perforation risk. This might be beneficial in women with severe pre-eclampsia where BP control antepartum is challenging despite multiple medications (265).

With regard to development and testing of a self-management intervention for postpartum antihypertensive adjustment this review did not find any evidence underpinning the use of particular

BP thresholds for medication adjustment postpartum, illustrating that those suggested by NICE are expert-derived (1). There is no clear evidence to support selection of a particular antihypertensive agent postpartum, only that the commonly used and recommended agents seem to be variably effective. No previously tested model of care demonstrated clear benefit in this population (197, 231), so development of a BP self-management intervention is reasonable, particularly in light of the effectiveness demonstrated in non-pregnant populations with essential hypertension (118, 119).

Chapter 3: Local audit and regional survey of postnatal hypertension management

3.1 Overview

This chapter describes the methods and findings from local preparatory work for the trial (Chapter 4), including an audit and a regional survey, both designed to evaluate existing practice. The survey was published as a short communication in *Pregnancy Hypertension* in October 2016 (Appendix 4) (272).

3.2 Objectives

Systematic review of the literature (Chapter 2) demonstrated a lack of good quality evidence in this area, which goes some way to explaining the sparse national and international guidance that exists for the management of postnatal hypertension (Chapter 1, Table 3). Therefore, prior to development and testing of a novel self-management intervention for antihypertensive treatment adjustment postpartum (Chapter 4), current local practice was evaluated.

The first step was to examine implementation of NICE guidance (1) in the local tertiary unit, which was planned to be the coordinating centre in the pilot study. The objective was to establish levels of adherence to the existing UK guidance, and a sense of what degree of standardisation of care exists. Following this, the objective was to gain a broader understanding of clinicians' opinions regarding postnatal BP management, across the local region, by undertaking an online survey.

An audit was designed to assess whether the care provided locally in secondary care, and in the community and primary care after discharge, for women with gestational hypertension or pre-eclampsia, who require ongoing antihypertensive treatment, was meeting the NICE standards set out in the Clinical Guideline (CG107) (1). The NICE Clinical Guideline was selected as the basis for the audit standards as it is the guideline most pertinent to practice in the UK. Furthermore, for the time period when the audit was conducted, the NICE recommendations for care during the postpartum period were the most detailed (Table 3), as the SOGC guideline had yet to be published (9). The overall objective was to establish whether the NICE guidance was an appropriate basis for design of

a self-management intervention, in terms of monitoring frequency, BP thresholds and approach to antihypertensive medication adjustment.

Due to the absence of robust evidence-based guidance (Chapter 2); to supplement the information gained by the audit; and to avoid imposing a strategy at odds with routine practice during the self-management pilot study (Chapter 4), a regional survey of healthcare professionals was conducted to establish normal clinical practice and inform standardised design of medication adjustment schedules. During the proposed pilot study, evaluating a novel self-management intervention for postpartum hypertension, participants in the intervention group required an individualised medication adjustment schedule. There is no formal guidance regarding adjustment of antihypertensive medications postpartum (Table 3). This is one of the challenges to development of a self-management intervention for this clinical scenario. To help guide creation of general principles on which to base medication adjustment schedules an understanding of healthcare professionals' current approach to this clinical scenario was sought.

3.3 Audit of postnatal hypertension management

This section describes the methods and results of a local audit of postnatal hypertension management conducted at the Oxford University Hospitals NHS Foundation Trust.

3.3.1 Audit: Standards

Current practice was measured against the criteria set out in the NICE Clinical Guideline. The NICE recommendations were subdivided under the headings: BP monitoring; antihypertensive treatment; care plans. NICE recommends 100% compliance with each criterion (sections 3.3.1.1 - 3.3.1.3).

In addition to information directly related to the NICE standards, the following data were collected:

- Medication(s) and dose(s) on discharge from hospital;
- Any medication increases after discharge;

- Total duration of medication;
- Details of any readmission(s) to hospital with problems related to BP.

3.3.1.1 *Blood pressure monitoring*

In gestational hypertension, NICE recommends monitoring BP daily for the first two days after birth and then at least once between day three and day five after birth. Beyond this, BP should be monitored as is clinically indicated if antihypertensive treatment is changed. In women with pre-eclampsia who took antihypertensive treatment during their pregnancy, the guidelines state that BP should be monitored at least four times a day whilst the woman is still an inpatient. After discharge from hospital BP should be monitored on at least alternate days for up to two weeks after until the woman is off treatment and has no hypertension. These monitoring frequencies are not based on any published literature (section 2.4.3.1). Additionally it is recommended that women should be asked about severe headaches and epigastric pain each time BP is measured.

NICE recommends offering women with pre-eclampsia discharge from hospital if all of the following criteria have been met: they are asymptomatic of pre-eclampsia; their BP, with or without treatment, is <150/100mmHg; their blood test results are stable or improving. The available evidence does not provide any information to support these recommendations, but observational data suggest that hypertension persists postpartum, for a mean duration in the region of 6 weeks (84), and that although BP often falls immediately after birth, this is commonly followed by a return to hypertensive levels (80).

The NICE guideline suggests the following structure for medical follow-up postpartum: medical review at two-weeks and six to eight-weeks postpartum. If women remain hypertensive requiring treatment at the six-week check, they should be offered referral to a hypertension specialist (1). A recently published review echoes this recommendation (273). However, this care structure is not supported by an evidence base: indeed there are only two studies in the literature evaluating different postpartum models of care in hypertensive women, which fail to provide a firm conclusion

(197, 231). The more recent Canadian guideline recommends specialist referral if problems persist three to six-months after birth (9).

3.3.1.2 *Antihypertensive treatment*

For postnatal women, with gestational hypertension or pre-eclampsia, the NICE guidelines state to continue antenatal antihypertensive treatment, and consider dose reduction if BP is <140/90mmHg. If BP is <130/80mmHg the dose of medication should be reduced. These recommendations are based on the diagnostic thresholds used for essential hypertension in the non-pregnant population (127), but no evidence has been identified relating to medication adjustment postpartum (section 2.4.3.2) (89). If a woman has taken methyldopa to treat hypertension during pregnancy this should be stopped within two days of birth, due to a concern about an association with an increased risk of postnatal depression (103).

The guideline suggests that women with HDP, who did not take antihypertensive treatment during their pregnancy, commence antihypertensive treatment if their BP is $\geq 150/100$ mmHg. This recommendation is based on the largely expert-derived BP threshold used during pregnancy for the initiation or increase of antihypertensive treatment (1). At the time of publication of the NICE guidance (2011), limited evidence underpinned this statement: the authors cite a small, open-label RCT examining treatment of diastolic hypertension with methyldopa at a threshold of 90-109mmHg versus ≥ 110 mmHg. This reported fewer episodes of severe hypertension in the intervention group, as well as a lower incidence of eclampsia with BP treatment in the lower range (8.8% versus 27.8%, $p < 0.05$) (274). Since publication of the NICE guideline, a large RCT (CHIPS) has been published examining tight (diastolic target 85mmHg) versus less-tight (target 100mmHg) BP control in pregnancy, reporting that the incidence of severe hypertension ($\geq 160/110$ mmHg) was significantly less common in the intervention group (tight control) (27.5% versus 40.6%, $p < 0.001$). No difference was seen between groups in adverse neonatal outcomes or overall maternal complications (275). A subsequently published, post-hoc analysis of these data concluded that severe hypertension is a risk

marker for adverse maternal and perinatal outcomes, independent of BP control or pre-eclampsia as a co-occurrence (276).

3.3.1.3 Care plans

Guidance suggests that women with HDP should have a written care plan given to them at discharge to community care. This care plan should include details regarding: who will provide follow-up care, including medical review if needed; frequency of BP monitoring needed; thresholds for reducing or stopping treatment; indications for referral to primary care for BP review. Additionally for women with pre-eclampsia the care plan should include advice about self-monitoring for symptoms. The NICE guideline does not cite any references underpinning this advice (1). However, some evidence does exist in other fields supporting the use of written handover plans, particularly when stepping down care in hospitals (277, 278).

3.3.2 Audit: Methods

A retrospective audit of 20 consecutive patients, who delivered at the John Radcliffe Hospital, Oxford, with a diagnosis of pre-eclampsia or gestational hypertension, and required antihypertensive medication upon discharge from hospital after birth, was conducted. Women were excluded if they had a diagnosis of chronic hypertension – defined as requiring antihypertensive medication outside pregnancy – as this cohort require a different management approach after birth. Usual practice would be to return them to their pre-pregnancy medication, provided it was safe for breastfeeding.

An audit form was designed to capture the data described in section 3.3.1 (Appendix 5). A coded database search of the hospital Electronic Patient Record® system was undertaken for women who delivered between August and September 2013 with pre-eclampsia, gestational hypertension or eclampsia. The search yielded 99 results.

The first consecutive 55 patients' maternity notes were reviewed to determine eligibility. 3/55 sets of notes were not found. From the remaining 52 sets of notes: 24/52 women had pre-eclampsia or gestational hypertension requiring ongoing medication postpartum; 1/52 had chronic hypertension medicated prior to pregnancy; 27/52 did not require postpartum antihypertensive treatment: they either never required medication or they had their antihypertensive medications stopped prior to discharge to the community. From this snapshot database search: 46% of women coded for a diagnosis of a hypertensive disorder of pregnancy, had pre-eclampsia or gestational hypertension requiring ongoing antihypertensive medication after discharge to the community postpartum.

The first consecutive 20 sets of notes were reviewed in detail (delivery date 03/08/2013-01/09/2013). Patients' GPs were contacted to obtain information about their care after discharge. Telephone contact was made successfully with 9/20 GPs. The remaining 11 GPs were written to with a questionnaire for them to complete and return (Appendix 6). 3/11 responses were received, such that post-discharge data was available for 12/20 patients.

3.3.3 Audit: Results

17/20 (85%) were discharged home on one antihypertensive medication. 3/20 (15%) were discharged home on two agents. Figure 7 illustrates the range of agents prescribed.

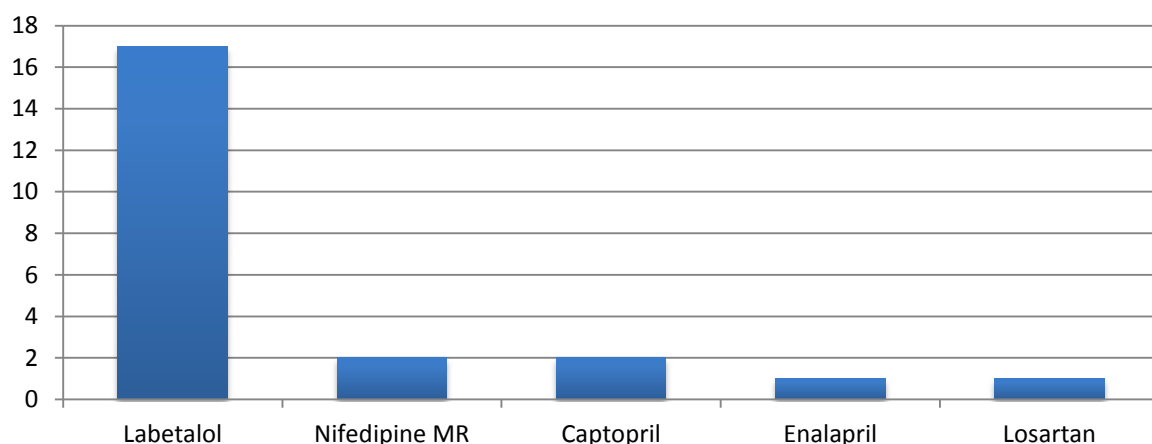


Figure 7: Antihypertensive medication prescription postpartum

1/12 (8%) GPs reported a medication increase after discharge from hospital. 1/12 (8%) GPs reported that their patient still required antihypertensive treatment at the time of the audit (May 2014). For the remaining 11 women, for whom this information was available, the mean duration of therapy was 51.9 days, with a range of 14 – 120 days (Table 12).

Table 12: Audit participant characteristics (n = 20, including one twin pregnancy)

		Mean (range)
Age /years		30.2 (19 – 42)
Birthweight /g		2909.9 (447 – 4290)
Gestation at delivery /weeks		37.5 (25.6 – 41.0)
Total length of hospital stay /days*		5.2 (2 – 13)
Time to discharge to midwifery led care /days†		5.0 (2 – 13)
Duration of medication /days (n = 11‡)		51.9 (14 – 120)
		n (%)
Diagnosis (n = 20)	Pre-eclampsia	10 (50%)
	Gestational hypertension	10 (50%)
Mode of birth (n = 21)	Spontaneous vaginal delivery	10 (48%)
	Vaginal breech birth	1 (5%)
	Assisted vaginal delivery	5 (24%)
	Caesarean section	5 (24%)
Delivery outcome (n = 21)	Live birth	19 (90%)
	Intrauterine death	1 (5%)
	Fetocide	1 (5%)

3.3.3.1 Blood pressure monitoring

In women with gestational hypertension, 10/10 (100%) had their BP checked on the first two days postpartum. 9/10 (90%) were documented as having had their BP monitored once between day three and five after birth. Data from GPs stated that 6/6 women (100%) had their BP monitored when treatment was changed.

Amongst the women with pre-eclampsia, 10/10 (100%) had their BP monitored four-times daily whilst they remained in hospital. No reliable data was obtained about alternate daily BP monitoring

* 1 patient self-discharged on day four postpartum

† In total there were four additional days in hospital after discharge to midwifery led care

‡ Excludes one woman on ongoing treatment

after discharge. It was documented that 9/10 (90%) had symptoms checked on the daily ward round, but 0/10 (0%) were asked about their symptoms each time their BP was measured.

11/12 (92%) had a two week and six to eight-week medical follow-up with their GP. Only 1/12 (8%) did not have a two-week check, and 1/12 (8%) did not attend their six to eight-week check. 4/12 (33%) remained on antihypertensive treatment at their six to eight-week follow-up visit, but none of these were referred to a hypertension specialist (Figure 8).

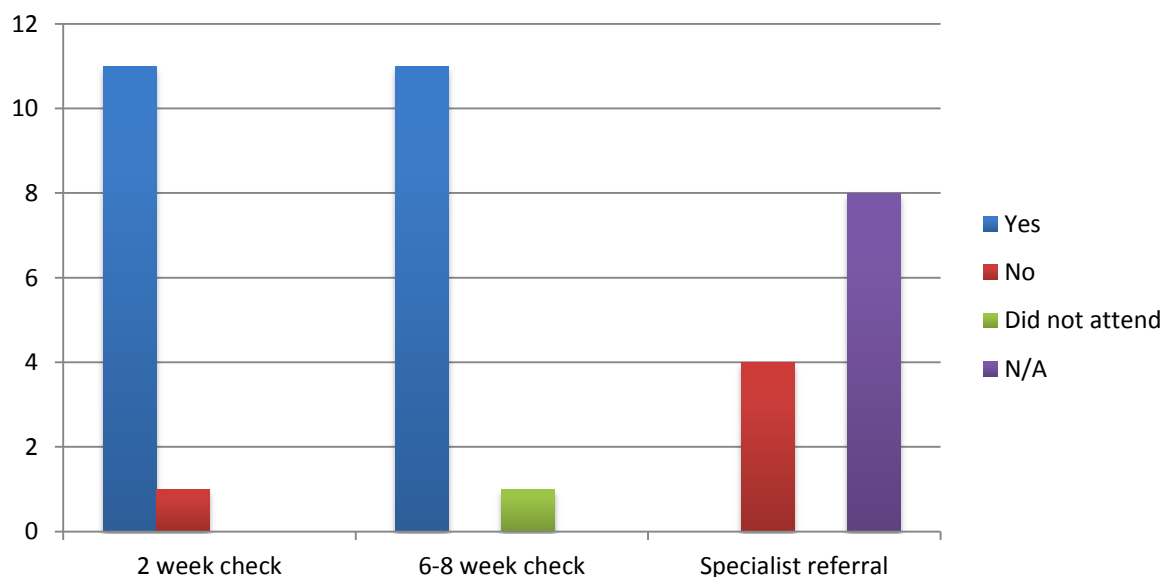


Figure 8: Medical follow-up postpartum

3.3.3.2 Antihypertensive treatment

Antenatal hypertensive treatment was continued in 15/20 (75%). The remaining 5/20 (25%) had antihypertensive treatment commenced during the postnatal period as their BP was 150/100mmHg or higher. Only 1/20 (5%) was taking methyldopa at the time of birth, and this was switched in the first 48 hours postpartum, as per NICE guidance.

In terms of treatment commencement or increase if the BP $\geq$ 150/100mmHg: this was not applicable in 7/20 (35%) for whom both hospital and community records were available, and there was no community data available for a three further cases. 10/10 (100%) who had a documented BP of

$\geq 150/100\text{mmHg}$, had treatment started or increased. For the definitive NICE recommendation that if BP postpartum is recorded as $<130/80\text{mmHg}$ treatment should be reduced or stopped: Where there was complete hospital and community data this was done appropriately in 9/12 (75%); this was not done in 1/12 (8%); in 2/12 (17%) it was not clear how this was managed from the data provided by their GP.

3.3.3.3 Care plans

In 18/20 (90%) documentation of a care plan for after discharge was identified in the hospital records. 6/12 GPs (50%) reported receiving a care plan when their patient was discharged from hospital. Figure 9 details what information was included in the care plans (both those in the notes, and those actually received by a GP).

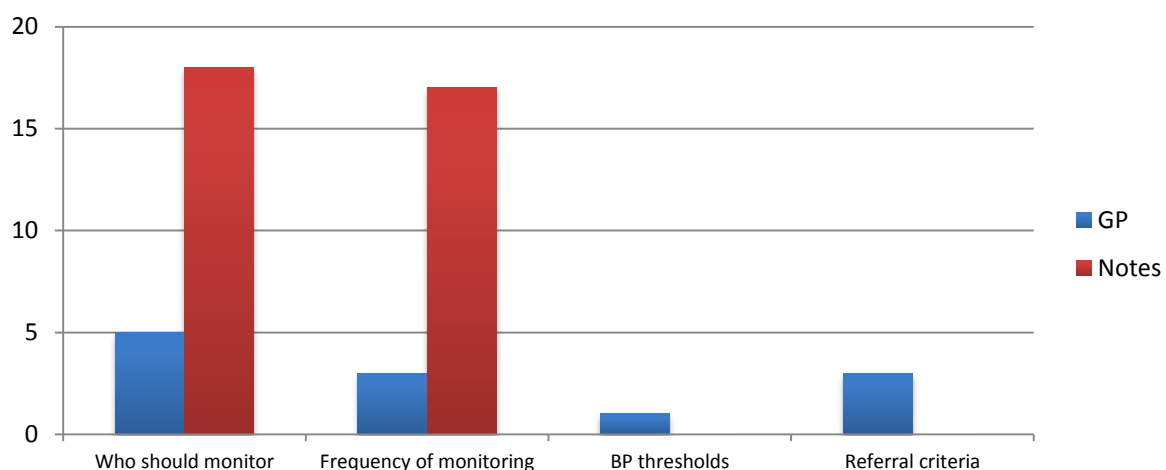


Figure 9: Details of care plans

3.4 Postnatal antihypertensive medication adjustment survey

This section describes the methods and results of a regional survey of postnatal hypertension management practices.

3.4.1 Survey: Research questions

- [1] Do clinicians have a preference for a particular antihypertensive medication for use in the postnatal period?
- [2] What BP thresholds do clinicians use when adjusting antihypertensive medications in the postnatal period?
- [3] When down-titrating antihypertensive medications, do clinicians reduce the dose by a certain proportion at a time?
- [4] When down-titrating multiple antihypertensive medications how do clinicians approach this?
- [5] Do the approaches used differ between different groups of clinicians?

3.4.2 Survey: Methods

A protocol was developed (Appendix 7) and ethical approval was obtained from the University of Oxford (MS-IDREC-C1-2015-019). An online survey of prescribing and non-prescribing clinicians, in primary and secondary care, was undertaken. Several NHS primary and secondary care centres were involved in the research study (Oxford University Hospitals NHS Trust, Royal Berkshire Hospitals NHS Foundation Trust, Northampton General Hospital NHS Trust, Buckinghamshire Healthcare NHS Trust, NIHR Clinical Research Network: Thames Valley and South Midlands). This study did not involve the use of any patient data, and no identifiable or confidential data about participants was recorded: the survey was completed anonymously. The following demographic data about respondents was collected: job role, place of work and age. Two questionnaires were designed: one for prescribing clinicians, and one for non-prescribing clinicians (Appendix 7). The first question of each survey asked participants to confirm that they had read the participant information sheet (Appendix 8) and that they agreed to take part in the survey.

The intention was to invite 300 clinicians to participate (200 prescribers, 100 non-prescribers), aiming for a 50% response rate (150 responses). Participants were invited to complete the

questionnaire by email (February – June 2015). The email contained a link to the online survey and the participant information sheet (Appendix 8) was attached. A reminder email was sent after three weeks.

The primary outcome was clinicians' preference for which antihypertensive medication to use postpartum: Participants were asked to list all the antihypertensive medications they would consider using postpartum and then to choose which they used most commonly. In the analysis, denominators were adjusted according to the number of participants who answered each question. Continuous variables are reported as means with standard deviations (or medians with interquartile ranges if skewed). Categorical variables are reported as counts and percentages. Differences between groups were calculated where appropriate but did not include significance tests with P-values, as the survey was not powered to allow this.

3.4.3 Survey: Results

3.4.3.1 Response rate

Survey invitations were sent to 262 prescribing clinicians (approximately half obstetricians and half GPs), and 128 non-prescribers (hospital and community midwives). Overall the response rate was 101/390 (26%): 81/262 (31%) prescribers and 20/128 (16%) non-prescribers (Table 13).

Table 13: Summary of invitations and responses for survey

	Invitations sent out	Responses
GPs	139	40 (29%)*
Obstetricians	123	41 (33%)
Midwives	128	20 (16%)
TOTAL	390	101 (26%)

* 5 further responders, but no details completed

3.4.3.2 Choice of antihypertensive medication

Table 14: Postpartum antihypertensive medication selection

	GPs		Obstetricians		Midwives		Total	
Labetalol	32	80%	39	98%	18	100%	89	91%
Nifedipine MR	10	25%	35	88%	14	78%	59	60%
Nifedipine	7	18%	19	48%	9	50%	35	36%
Captopril	4	10%	23	58%	6	33%	33	34%
Enalapril	4	10%	17	43%	1	6%	22	22%
Amlodipine	5	13%	10	25%	1	6%	16	16%
Doxazosin	2	5%	12	30%	1	6%	15	15%
Atenolol	4	10%	10	25%	1	6%	15	15%
Metoprolol	5	13%	5	13%	0	0%	10	10%
Other [†]	9	23%	0	0%	1	6%	10	10%
Alpha-methyldopa	2	5%	2	5%	4	22%	8	8%
Metoprolol MR	2	5%	3	8%	0	0%	5	5%

Table 15: Commonest postpartum antihypertensive medication

	GPs (n = 40)		Obstetricians (n = 41) [†]		Midwives (n = 20) [§]		Total	
Labetalol	27	68%	38	95%	18	100%	83	85%
Atenolol	2	5%	2	5%	0	0%	4	4%
Metoprolol	3	8%	0	0%	0	0%	3	3%
Other ^{**}	3	8%	0	0%	0	0%	3	3%
Captopril	2	5%	0	0%	0	0%	2	2%
Nifedipine MR	2	5%	0	0%	0	0%	2	2%
Enalapril	1	3%	0	0%	0	0%	1	1%
Nifedipine	0	0%	0	0%	0	0%	0	0%
Amlodipine	0	0%	0	0%	0	0%	0	0%
Doxazosin	0	0%	0	0%	0	0%	0	0%
Alpha-methyldopa	0	0%	0	0%	0	0%	0	0%
Metoprolol MR	0	0%	0	0%	0	0%	0	0%

Labetalol was by far the most commonly used antihypertensive, with 89/98 (91%) stating that they would use it during the postnatal period (Table 14), and 83/98 (85%) selecting it as the agent they would use most commonly (Table 15). Nifedipine – both standard and modified release – was the

[†] 9 GPs commented that they would not commence a new agent, but would continue the medication that had been started by the patient's obstetric team. 1 midwife selected labetalol and also 'other' commenting that she had not worked in the postnatal area for 12 years.

[‡] Only 40 responses to this question

[§] Only 18 responses to this question

^{**} 2 GPs commented that they rarely or never encountered this problem in their clinical practice. 1 GP stated they would continue what they had been taking during pregnancy.

next most commonly selected antihypertensive when clinicians listed all the agents they might utilise postpartum. A small number of clinicians reported using methyldopa postpartum, more commonly non-prescribers: 4/18 (22%) versus 4/80 (5%), difference between groups 17%.

3.4.3.3 Blood pressure thresholds for medication adjustment

The NICE guideline recommends considering reduction of antihypertensive medication when BP <140/90mmHg, and states that medication should definitely be reduced once BP <130/80mmHg.

The guideline suggests increasing or commencing medication if the BP ≥150/100mmHg(the same threshold recommended by NICE during pregnancy) (1). The aim was to ascertain whether these are the thresholds being used in clinical practice, and whether there was any difference in the BP thresholds used for medication adjustment by the different groups of clinicians.

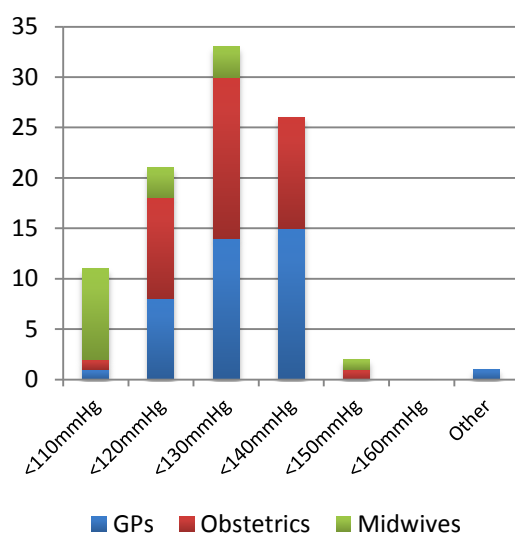


Figure 10: Systolic blood pressure thresholds for medication reduction

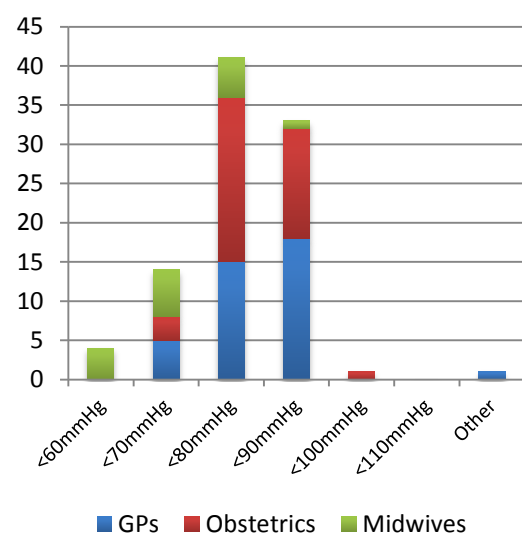


Figure 11: Diastolic blood pressure thresholds for medication reduction

Clinicians were asked to select the highest SBP and DBP thresholds (separately) at which they would first consider reducing the dose of antihypertensive medication (Figure 10 and Figure 11). Overall 59/94 (63%) selected a SBP, and 74/94 (79%) a DBP in line with NICE guidance (130-140/80-90mmHg). Midwives selected lower thresholds than did prescribing clinicians: 12/16 (75%) selected a SBP of 110-120mmHg compared to just 20/78 (26%) prescribing clinicians, difference between

groups 49%. 10/16 (63%) a DBP of 60-70mmHg versus 8/78 (10%) prescribing clinicians, difference between groups 53%.

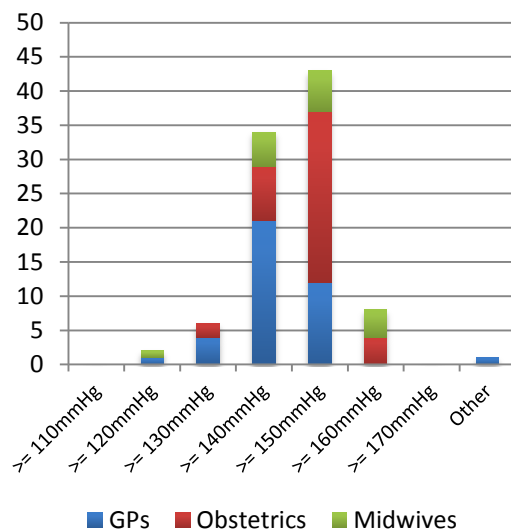


Figure 12: Systolic blood pressure thresholds for medication increase

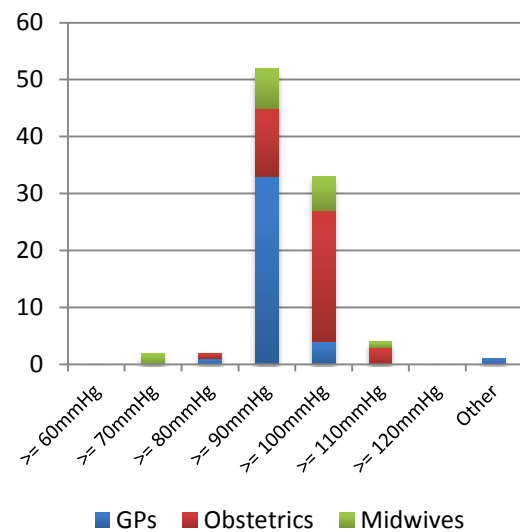


Figure 13: Diastolic blood pressure thresholds for medication increase

Participants were asked to select the lowest SBP and DBP thresholds (separately) at which they would first increase the dose of antihypertensive medication (Figure 12 and Figure 13). Fewer participants responded in line with NICE guidance: 43/94 (46%) selected a SBP of $\geq 150\text{mmHg}$ and 33/94 (35%) selected a DBP of $\geq 100\text{mmHg}$. In this case, GPs tended to select lower thresholds than did the obstetricians (Figure 12 and Figure 13): 25/39 (64%) GPs selected a systolic threshold of ≥ 130 or $\geq 140\text{mmHg}$ versus 10/30 (26%) obstetricians, difference between groups 38%. 34/39 (87%) GPs selected a diastolic threshold of ≥ 80 or $\geq 90\text{mmHg}$, compared to 13/39 (33%) obstetricians, difference between groups 54%.

3.4.3.4 Approach to down-titration

Prescribing clinicians were asked to state how they would reduce the dose of an antihypertensive medication when down titrating in response to low BP. A diverse range of responses was given (Figure 14), but the most commonly selected answer was that it would depend on the patient's BP 25/78 (32%). The second commonest response was that the decision would be based on the

prescribing formulary 19/78 (24%). The responses were heterogeneous regardless of the specialty of the respondents. Both prescribing and non-prescribing clinicians were asked about their view of how down-titration of multiple medications should be approached (Figure 15). Again the responses were varied although 45/94 (48%) stated that they would reduce one medication at a time.

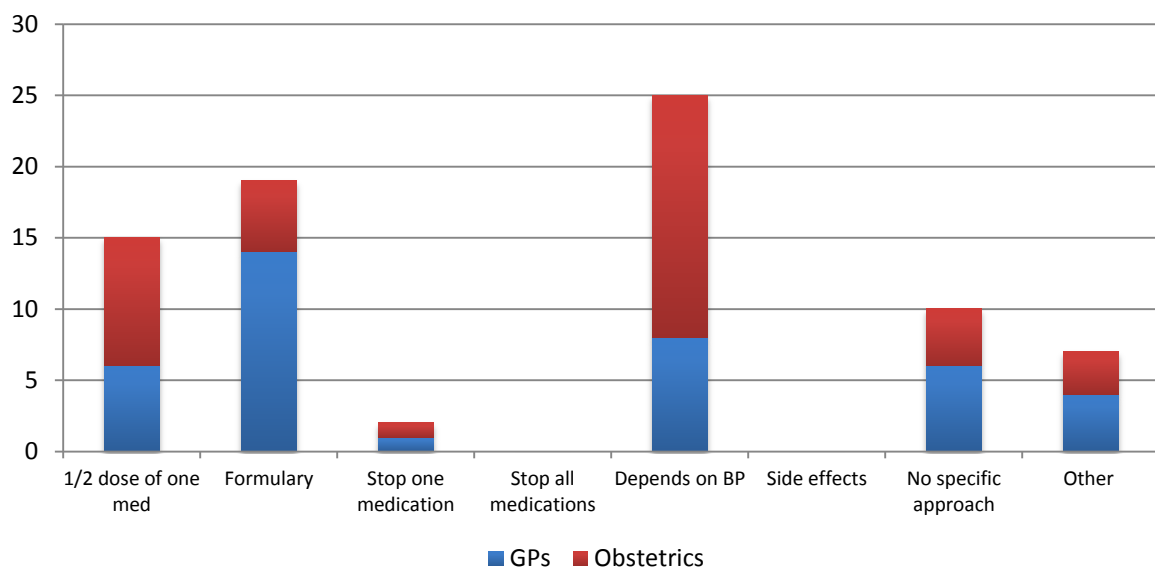


Figure 14: Approach to down-titration

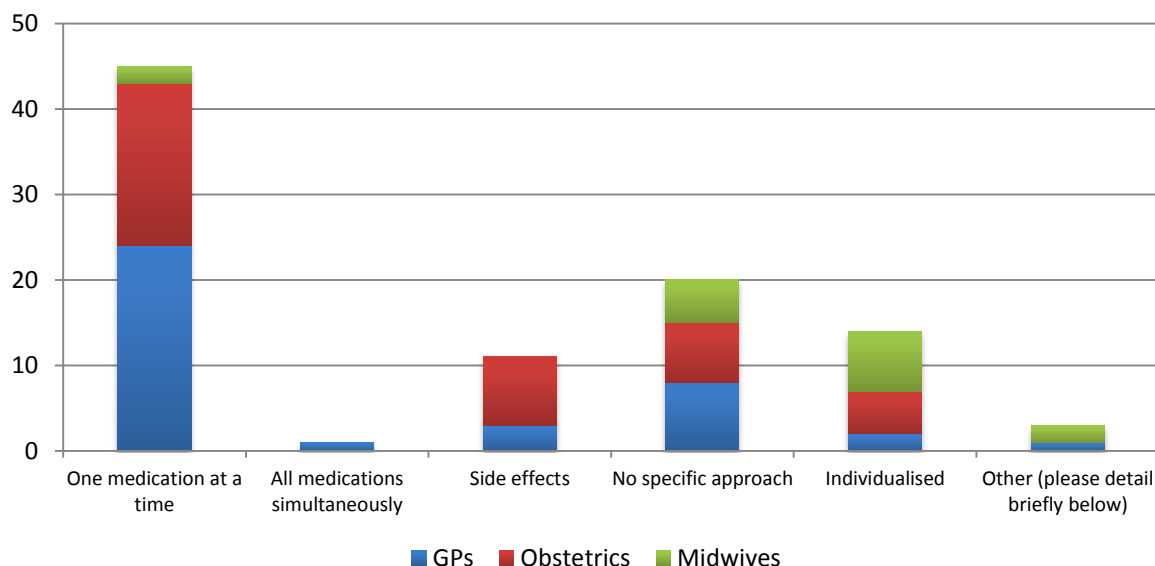


Figure 15: Approach to down-titration of multiple medications

3.5 Discussion

Overall these results suggested considerable heterogeneity in current management of hypertension postpartum, which may reflect the lack of evidence and guidance in this area. Where clear recommendations do exist, practice seemed to be more consistent.

In the audit, monitoring of BP was in general done well (where data was available), and almost all patients had the recommended two and six to eight-week follow-up medical appointments with their GP. The audit results suggested medication was adjusted appropriately using the NICE thresholds, although it was not always documented that these thresholds were being used as a basis for the decision-making. This was echoed by the survey findings where there was reasonable consistency in the BP thresholds clinicians reported using for medication adjustment, albeit, in the case of up-titration, more from obstetricians than GPs. This may be reflective of obstetricians' familiarity with use of the same threshold for medication commencement or increase during pregnancy.

From the survey labetalol was overwhelmingly the most commonly utilised antihypertensive medication postpartum, with nifedipine the second commonest when clinicians listed all agents they might use, in line with the NICE guidance (1). However, a small number of clinicians did report using methyldopa postpartum, although none selected it as the agent they would use most commonly. This contravenes the recommendation from NICE that methyldopa be stopped within 48 hours of birth due to concerns about increasing the risk of postnatal depression (1, 103). This response was more common amongst non-prescribers (22% versus 5%), which might be expected given that responsibility for altering a prescription does not lie with them. Only one patient in the audit cohort was taking methyldopa at the time of birth, and this was switched appropriately after delivery.

Some areas for improvement were identified from the audit results: Symptom monitoring in pre-eclampsia was done on ward rounds, but there was no documentation of symptom monitoring with each BP check. It is possible that during these checks the midwives do in fact ask patients about

symptoms, but that this is not documented in the notes. Women with PET should be advised of the importance of symptom monitoring after discharge, and this discussion should be documented in the notes and the postnatal care plan. In the audit amongst the four women who remained hypertensive, and required ongoing medication, at the six-week postnatal check, none were referred for specialist assessment of their BP. Care plans were only received by 50% of GPs, despite being documented in the hospital records in 90% of cases. Furthermore, the level of details in these plans was variable and fell far short of that recommended by NICE. The specific recommendations made locally that were made following the audit are detailed in Table 16.

No guidance exists regarding how to reduce antihypertensive medications postpartum, or how to adjust multiple medications, so it is perhaps not surprising that there were a wide range of responses from all groups in response to these survey questions. Such diversity may result in patients receiving different advice from different healthcare professionals, with potentially negative consequences for continuity of care. It may also result in differing standards of care across different NHS settings.

Table 16: Audit recommendations

Blood pressure monitoring	Document monitoring of symptoms in midwifery notes
Care plans	Adapt blood pressure letter to GPs to include:
	Frequency of monitoring
	Who should provide care
	Blood pressure thresholds for medication adjustment
	Indications for referral to primary and secondary care
	Advice to offer referral to Hypertension specialist if remain on treatment at six to eight-week check
	Use blood pressure letter for all patients, not just patients under the care of the high risk obstetric team

A strength of the audit is that it attempted to obtain data from the community as well as from hospital records. Similarly the survey was strengthened by the broad spectrum of healthcare professionals surveyed, across a range of different settings, including both district general and teaching hospitals, urban and rural primary care centres. However, both the audit and survey were

limited by small sample sizes and low response rates. Only 20 cases were audited, and a limited response was received from GPs when audit data was requested, with only a 55% response rate despite using both telephone and postal questionnaires. Furthermore it was not possible to obtain audit data about frequency of BP monitoring by community midwives. The survey also had a low response rate (Table 13), and a relatively small total number of responses (101 individuals). This might bias the results towards the opinions of clinicians with more interest or expertise in this area, rather than obtaining a true cross-sectional view.

Traditionally, women with gestational hypertension and pre-eclampsia receive a very intensive level of care in the antenatal and intrapartum periods. This usually extends into their postnatal hospital stay, but due to a poor level of communication with GPs and community midwives, the care of women after discharge might be patchier. Research suggests that BP control in this period may have implications in terms of both immediate complications and women's long-term cardiovascular health (111). In addition to the local recommendations made, this audit, coupled with the survey data, support the need for additional research about how to manage women with hypertension postpartum in order to optimise BP control and improve patient experience. Research is needed to formulate uniform approaches to BP monitoring and medication down-titration, and to streamline handover from secondary to primary care. One potential solution – effective in essential hypertension – could be BP self-management, using validated home BP monitors and a standardised algorithm for medication adjustment (118). The data presented, in this chapter, support the development and testing of a self-management intervention for use by this population.

Information from the coded electronic database search was useful in planning the sample size and recruitment period for the pilot study (section 4.5.2.6): approximately 25 women per month across the two Oxford University Hospitals NHS Foundation Trust sites would be potentially eligible for the study (gestational hypertension or pre-eclampsia requiring ongoing antihypertensive medication after birth). The data regarding BP thresholds used for medication adjustment, suggested that basing

a down titration algorithm on the thresholds recommended by NICE would be a reasonable strategy, which would not conflict with practice in the local region. Furthermore, the survey and audit data regarding drug selection postpartum allowed consideration of which agents to include when planning medication adjustment schedules (section 4.3.3). As regards how to reduce medication; no consistent method was revealed by the survey data. However, the answers yielded by the survey provided a basis from which to begin considering how to create a standardised approach for adjustment schedules, and were reassuring in terms of trying to avoid imposition of a management strategy at odds with usual clinical practice.

Chapter 4: Self-mANagement of Postnatal antiHypertensive Treatment: the SNAP-HT open-label randomised controlled pilot trial

4.1 Overview

This chapter describes the development and testing of a novel self-management intervention for postnatal antihypertensive treatment (section 4.3), pilot trial set-up (section 4.4), methods, results and conclusion (section 4.5). For the trial the author was the Chief Investigator (CI) and the Trial Manager.

4.2 Objectives

In view of the paucity of evidence (Chapter 2), and lack of consensus amongst clinicians (Chapter 3), regarding appropriate management of hypertension postpartum, the intention was to develop a self-management intervention for use by women with treated HDP during the postnatal period. This was based on experiences with self-management of essential hypertension using telemonitoring, where this was shown to be safe, effective and acceptable (118, 119). A multicentre, open-label pilot RCT (SNAP-HT) was developed to test the feasibility and acceptability of the intervention, and gather preliminary efficacy and safety data.

Self-management of BP has the potential to help standardise postpartum management for women with HDP, in line with recent suggestions from the Chief Medical Officer (77). Normalisation of BP postpartum has an unpredictable trajectory (83), which necessitates an individualised approach to down-titration, involving regular BP monitoring: a single 'one-size fits all' approach, as is taken with, for example, the down-titration of oral corticosteroids, is not appropriate. Furthermore, self-management may reduce the time burden for patients in terms of GP and midwife appointments in the postnatal period, and have cost-saving implications for the NHS. There is some qualitative evidence supporting the theory that self-management can empower patients and make them feel more confident and in control of their medical condition (279).

4.3 Intervention development

The hypothesis underpinning this study was that self-management techniques utilised successfully in populations with essential hypertension, in the TASMINH2 (118) and TASMIN-SR (119) RCTs, could be applied equally successfully to postnatal women with HDP leading to better control of BP. The aim was to combine these experiences and expertise, along with knowledge gained from related pilot work using self-monitoring in higher risk women to detect new-onset hypertension during pregnancy (BuMP pilot study), into development of a novel self-management intervention for reduction and cessation of antihypertensive medications postpartum.

As yet, there are little data to support a role for self-monitoring or even self-management in women with gestational hypertension or pre-eclampsia during pregnancy or postpartum (section 1.9.3) (141, 280). Presently when women with HDP are discharged from hospital after birth their care is transferred to their community midwives and GPs. As described in the previous chapters, national and international guidance regarding postnatal monitoring is scarce (Chapter 1, Table 3) as is the evidence underpinning it (Chapter 2). The preliminary audit and survey (Chapter 3) suggested that handover of care; frequency of BP monitoring and the approach to medication adjustment were variable. Self-management, proven to be effective in BP lowering in essential hypertension (118, 119), was proposed as a potential solution to streamline, standardise and improve care.

Self-management of hypertension is a complex intervention (section 1.10) involving the following components (sections 4.3.1 to 4.3.7): HBPM; BP thresholds for medication adjustment and seeking medical attention; medication adjustment schedules; telemonitoring for submission of readings and receipt of instructions; feedback to participants and clinicians and measures to ensure participant safety; participant and staff training.

The self-management intervention for the SNAP-HT trial was based on those utilised in the TASMINH2 and TASMIN-SR trials (118, 119), designed to achieve better BP control in the context of poorly controlled essential hypertension. Therefore some key differences needed to be addressed

during design of the SNAP-HT self-management intervention. These adaptations were made in consultation with the Trial Management Group (TMG) (section 4.4.4). Advice was also sought from an experienced pharmacologist. The adaptations for each component of the intervention are described in sections 4.3.1 to 4.3.5 and were carefully tested (section 4.3.6) prior to implementation in the pilot.

4.3.1 Home blood pressure monitoring

The intention was to adapt the HBPM approach utilised by the TASMIN trials, in order to produce a monitoring schedule feasible for women with a new baby, which was sufficiently sensitive to the potentially rapidly changing BP during the puerperium (section 1.7.1).

In the TASMINH2 trial the participants utilised a home monitor (OMRON 705IT), which has not been validated for use in pregnancy (as is the case for the majority of home BP monitors (281)). The TASMIN-SR trial, however, utilised the Microlife WatchBP® Home device, an automated oscillometric device, which has been validated for use in pregnancy and pre-eclampsia according to the British Hypertension Society protocol (130), and achieved grade A/A in pregnancy, and grade B/A in pre-eclampsia (128), and was therefore selected. Prior to study commencement the calibration of all monitors was confirmed by the CI using the PA350 Digital BPM Tester in line with a pre-defined testing schedule.

Frequency of monitoring in both TASMIN trials took the same format: two measurements daily, at a five-minute interval, for the first week of each month, with the second reading submitted. This design was ideally suited to the monitoring of a chronic condition, expected to persist. However, the clinical scenario in HDP postpartum is rather different: the expectation is that the majority of women will normalise over the weeks or months following birth, and therefore spaced periods of intensive monitoring are inappropriate. NICE recommend a minimum of monitoring on alternate days until day 14 postpartum, or treatment cessation, whichever is the longer, in pre-eclampsia (1). As HBPM had not been previously tested in this population, and it is recognised that rapid BP shifts can occur

(section 1.7.1), a more intensive monitoring schedule was felt to be preferable, and daily monitoring whilst taking antihypertensive treatment was settled upon. As in the TASMIN trials, participants were asked to take two readings and submit the second. In line with guidance from the European (125) and American (126) Societies of Hypertension, the minimum prescribed interval between the two readings was shortened to one minute, acknowledging the challenges women with a new baby might face in setting aside time to measure their BP.

Participants were asked to measure their BP once a day, at the same time each morning, whilst they remained on antihypertensive treatment. They were asked to take two readings, at least one minute apart, and to communicate the second reading via the telemonitoring service. Once antihypertensive treatment was stopped they were asked to continue daily readings, until they had five consecutive daily readings <140mmHg systolic and <90mmHg diastolic (aiming to ensure BP had completely settled), at which point they were instructed switch to weekly readings for the remainder of the trial period. If BP then rose to hypertensive levels again, participants were instructed to see their GP.

4.3.2 Blood pressure thresholds

To allow reduction and cessation of antihypertensive medication in line with falling BP postpartum, as well as appropriate referral to healthcare services in the event of a rising BP, or BP readings outside safety thresholds, an algorithm to classify all submitted BP readings was developed from those used in the TASMIN trials.

Both TASMIN trials utilised a colour traffic light system for the classification of home BP readings. Green indicated readings within the target thresholds. In TASMINH2 these were <130/85mmHg in non-diabetics, and <130/75mmHg in diabetics or those with chronic kidney disease (and >100mmHg systolic in both cases) (118). In TASMIN-SR the participants were all considered high risk for stroke, so the target was <120/75mmHg (119). In line with guidance from NICE and the British Hypertension Society, these targets were adjusted from the office targets – 10mmHg reduction in systolic, and

5mmHg reduction in diastolic (127). Amber signified readings above target, but not outside safety thresholds. In both trials having two consecutive months where ≥ 4 readings were above target triggered a medication change. Red denoted readings outside safety thresholds ($>200/100$ mmHg for TASMIN2, $>180/100$ mmHg for TASMIN-SR, and <100 mmHg systolic in both trials). The BP thresholds selected for medication adjustment, or for referral to a healthcare professional, in SNAP-HT (Table 17 and Table 18), were adapted from NICE (1). The colour chart developed for participants on treatment required more levels than needed in the TASMIN trials, to allow down-titration and appropriate referral for medical advice in the event of rising BP, so a rainbow chart was designed (Table 17).

In essential hypertension a BP of 135/85mmHg at home is considered equivalent to an office measurement of 140/90mmHg (127). There is limited evidence regarding whether different BP thresholds should be used for HBPM and office BP monitoring in pregnancy (280). To account for this uncertainty, the more conservative of the two BP thresholds NICE suggests for reduction of medication dose was used: NICE suggests considering down titration at a BP of $<140/90$ mmHg and definite reduction when the BP is $<130/80$ mmHg. The self-management algorithm developed for use in this pilot study reduced the medication dose when the BP was $<130/80$ mmHg on two consecutive readings (12-60 hours apart). The number of consecutive daily readings under the recommended threshold required to trigger a reduction in medication dose was agreed by consensus of the TMG (section 4.4.4), as NICE does not make this recommendation.

Given the potential for the SBP and DBP to fall under different thresholds (Table 17) for any given BP measurement, it was critical that the algorithm behaved in such a way that each BP measurement always fell into the single, most appropriate category so the following rules were constructed:

- [1] The most 'severe' case should always be returned;
- [2] The categories are ranked as follows (from 'most' to 'least severe'): very high, high, raised, low, high normal, low normal (on treatment)/normal (off treatment);

[3] For the high ranges (very high, high, raised, high normal) either reading is significant, so 'OR' is used;

[4] For the normal / low ranges (normal, low normal, low) both readings need to fall into this category, so 'AND' is used.

For readings that would trigger a response recommending the participant to seek medical attention (very high, high or low), the participant was asked to sit quietly for five minutes and repeat the reading to avoid excessive false positives (for example a high reading is due to the 'white coat' effect, or a low reading is because a participant has just woken up). If participants did not send a repeat reading within 10 minutes, the system accepted and responded to the original reading. If participants submitted additional readings these were subject to the same safety assessment. Additional readings <12 hours apart did not count towards the blue (low) readings contributing to a medication change. If a subsequent reading <12 hours after a blue reading was higher than a blue reading (i.e. green or above) this cancelled out the original blue reading.

Table 17: Blood pressure thresholds for self-management (on treatment)

Colour	Level	Blood pressure	Action
Red	Very high	Sys ≥ 160 OR Dia ≥ 110 OR Symptoms	Repeat blood pressure in 5 minutes. If this is a repeat reading: contact local maternity unit immediately for urgent assessment today.
Orange	High	Sys 150-159 OR Dia 100-109	Repeat blood pressure in 5 minutes. If this is a repeat reading: contact GP or midwife urgently for assessment today.
Yellow	Raised	Sys 140-149 OR Dia 90-99	No action.
Green	High normal	Sys 130-139 OR Dia 80-89	No action.
Blue	Low normal	Sys 100-129 AND Dia <80	If two days in a row follow medication change instructions.
Purple	Low	Sys <100 AND Dia <80	Repeat blood pressure in 5 minutes. If this is a repeat reading: contact GP or midwife urgently for assessment today.

Table 18: Blood pressure thresholds for self-management (off treatment)

Colour	Level	Blood pressure	Action
Red	Very high	Sys $\geq$ 160 OR Dia $\geq$ 110	Repeat blood pressure in 5 minutes. If this is a repeat reading: contact local maternity unit immediately for urgent assessment today.
Orange	High	Sys 140-159 OR Dia 90-109	Repeat blood pressure in 5 minutes. If this is a repeat reading record an orange reading. If 2 or more consecutive readings in this range contact GP for review within 48h.
Green	Normal	Sys <140 AND Dia <90	No action.

4.3.3 Medication adjustment schedules

In the TASMIN trials, all patients started above target and their GP devised an up-titration plan in the event of BP readings remaining high, consisting of a limited number of steps (two in TASMINH2 and three in TASMIN-SR). Given the broad range of drugs used in essential hypertension, and the widely differing prescribing practices amongst GPs, no attempt was made to standardise these steps between patients and a step could involve increasing the dose of a current medication or adding a new drug. Once the steps had been utilised, participants whose BP remained above target saw their GP to have a new set of steps created.

In postpartum hypertension, these constraints were less: a much smaller number of medications are utilised due to limitations with respect to breastfeeding (section 3.4.3.2); and most women are expected to normalise over weeks to months (section 1.7.1). Therefore it seemed reasonable to aim to completely down-titrate medication without medical input. No direct guidance is currently provided about the optimum way to manage this down-titration (Chapter 1, Table 3) and little consistency was identified amongst healthcare professionals (section 3.4.3). A standardised method by which to create individual down-titration schedules during the trial was devised in conjunction with the TMG (section 4.4.4) in consultation with an experienced pharmacologist.

The NICE adult hypertension guideline suggests commencing antihypertensive medication in the following order: ACE-inhibitor, calcium-channel blocker, diuretic, beta-blocker / alpha-blocker (127).

In the absence of an evidence-based method for drug withdrawal, it seemed appropriate to step-

down in the reverse order to that recommended for medication increase. Thus, given that diuretics are not prescribed for hypertension postpartum, this equates to alpha-blockers, beta-blockers, calcium-channel blockers and lastly ACE-inhibitors in terms of the order to reduce. To keep things simple, and in the absence of evidence to guide the decision, the TMG considered that halving the dose of one medication in each titration step was appropriate.

Both before trial commencement with the TMG, and during the trial with the Data Monitoring and Ethics Committee (DMEC) (section 4.4.5), the issue of whether to include up-titration steps, in the algorithm, was discussed at length. Women with high BP may be better detected by more frequent self-monitoring, compared to reliance on office measurement leading to a potential bias in readmission. Up-titration was suggested as a means of combatting the potential for increased postnatal readmission in the intervention group. After further review with the TMG (section 4.4.4), this was decided against for the following reasons: there was limited prior experience with self-management approaches in this population, so it was felt safer to involve a participant's direct care team in cases where the BP was too high, especially as a rising BP after hospital discharge is outside the expected norm. Producing bi-directional titration schedules would have significantly increased their complexity, and it was thought inappropriate to do this partway through the study. Lastly, it was relatively straightforward to produce a pre-defined down-titration schedule from an existing prescription, whereas producing a 'one-size fits all' solution to a potential future problem was viewed to be less valid.

The final, agreed standardised method for producing medication adjustment schedules was as follows:

- [1] Reduce / stop medications in the following order: alpha-blockers, beta-blockers, calcium-channel blockers, ACE-inhibitors;
- [2] Reduce one medication at a time and approximately halve the dose on each step until at the minimum dose then stop;

- [3] Medication adjustment schedules should only involve down-titration steps. Should a medication increase be required, the participant's direct care team should be involved immediately and then a new plan created with the new medications as the first step.

During the feasibility study, medication adjustment schedules were created by the CI, based on the participant's medications at discharge from hospital after birth, and were agreed with the participant's direct care team. Automation of this process is being considered for future trials.

When registering a participant on the telemonitoring website at the baseline visit, the researcher was required to input the participant's discharge antihypertensive medication(s), including dose and frequency. Following registration, the CI received an automated email to inform them a participant had been registered, and was then be able to create the medication adjustment schedule. It was then possible to create further schedules should they be required, for example if the direct care team altered a participant's medications, or if the dose needed to be increased after starting to decrease (as steps could only be used once – it was not possible to go backwards).

The telemonitoring service (section 4.3.4) automatically checked that participants' recorded current medications were consistent with what they are actually taking. This happened weekly, and the day after a medication change/stop message (Table 21). If a participant responded indicating their medications were not consistent this triggered the research team to contact them.

4.3.4 Telemonitoring

To support participants in self-managing their BP, i.e. allow submission of BP readings and receipt of feedback including medication down-titration instructions, a telemonitoring system was established. This was developed from ongoing work in essential hypertension (TASMINH4) where participants send BP results and receive automated replies following a predefined protocol dependent on level of BP (282). A mobile phone-based system was developed in collaboration with the Institute of Biomedical Engineering, University of Oxford. The author developed the specification and testing

schedule for this system, whilst the engineering department developed the technology. Participants were able to access a series of different tools to assist with self-management (Figure 16). These were all based on the same algorithm (section 4.3.2), and were extensively tested in the same way prior to implementation (section 4.3.6).

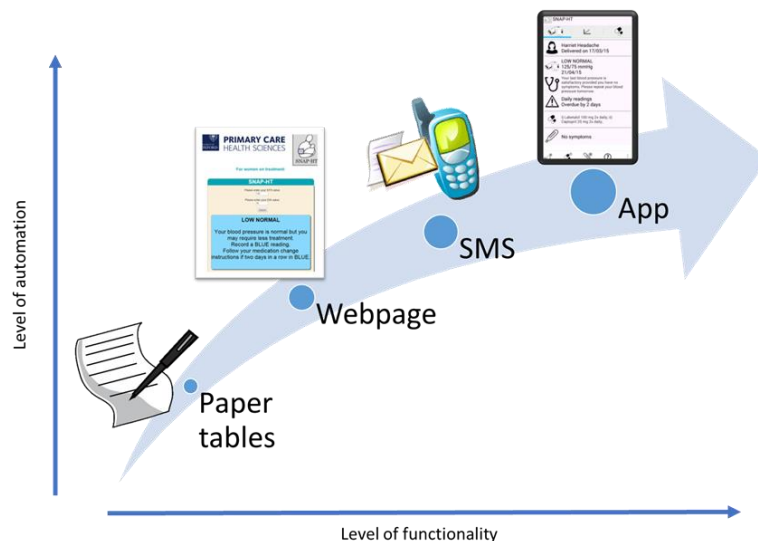


Figure 16: Overview of telemonitoring service

The simplest implementation of the algorithm was the rainbow charts (Table 17 and Table 18). Participants were provided with laminated copies of these charts, in order to be able to determine what category their BP readings fell into. This aimed to enhance participants' understanding, whilst serving as a fall back mechanism in the event of any technology failure. A web version of these tables was also developed by the Clinical Trials Unit (CTU) (<https://ctu2.phc.ox.ac.uk/snapht>). This allowed participants to input their BP reading and get an immediate response as to its category, without any need to log on or input any additional data. This removed any need for the participant to implement the 'AND' and 'OR' rules detailed in section 4.3.2, Table 17 and Table 18, as they were automatically applied to the BP reading by the web-tool. Neither the paper and web-based tools directly suggested what medication should be taken, nor did they take into account the current titration step, simply providing static information.

Participants were able to use either a SMS service (section 4.3.4.1) or a smartphone app (section 4.3.4.2) to submit their readings, receive feedback including down-titration instructions, respond to medication checks (section 4.3.3) and report symptoms and/or adverse events (section 4.3.5.2). The telemonitoring system automated the down-titration steps from a participant's medication adjustment schedule (section 4.3.3), such that once participants submitted two consecutive 'blue' readings (Table 17; <130mmHg systolic and <80mmHg diastolic) they were sent a message detailing how to step-down (or stop) their antihypertensive medication. It rejected nonsensical BP readings: systolic readings <30 or >300mmHg, and diastolic readings <20 or >250mmHg.

4.3.4.1 SMS Service

Table 19: Automated SMS responses

Response to yellow / green / first blue reading (on treatment) OR first orange / green reading (off treatment)	Thank you for your last reading: SYS/DIA. Your blood pressure is satisfactory provided you have no symptoms. Please repeat your blood pressure tomorrow.
Initial response to red reading (on or off treatment) OR orange / purple reading (on treatment)	Please sit quietly for 5 minutes and repeat your blood pressure, and then re-enter the repeat values.
Response to repeat red reading (on treatment)	Please contact your local maternity unit immediately and arrange urgent assessment today.
Response to repeat orange reading (on treatment)	Please contact your GP or midwife urgently and arrange assessment today.
Response to second consecutive orange reading (off treatment)	Please contact your GP or maternity assessment for review within 48 hours.
Response to second consecutive blue reading (on treatment)	Medication change. New treatment: i)Nifedipine M/R 20mg TDS; ii)Enalapril 20 mg OD (before going to sleep). (Structure is: **drug no. ** **drug name** **dose** **frequency** **notes**)
Stopping treatment	Medication change. Please stop taking all blood pressure medications now.
Switching to weekly readings	Thank you. Your blood pressure readings have all been normal since stopping treatment. Please change to once weekly readings.
Medication check (on treatment)	Your current treatment is i)Nifedipine M/R 20mg twice daily; ii)Enalapril 20 mg once daily; Is this correct? (Structure is: **drug no. ** **drug name** **dose** **frequency**)
Medication check (off treatment)	Please confirm that you are now off all blood pressure treatment. Is this correct?
Reminder message	We haven't received a BP reading since HH:MM on DD MMM. Please send us a new BP reading. For any problems please contact 08009150045. Thank you. Dr Cairns.
Rejection message	Sorry, the BP values you have sent are outside the range recognised by the system. Please check and either re-send or repeat your blood pressure. If you are having problems please contact the study team. Thank you.

The SMS service required participants to send an SMS to a Freephone number in a pre-defined format. Participants were able to submit BP readings ('BP SYS DIA' e.g. 'BP 130 80'), respond to medication checks ('BP med yes' or 'BP med no') and report adverse events ('BP symptom ***' e.g. 'BP symptom headache'). When a participant sent a BP reading they received an automatic, individualised response depending on the BP level, previous BP readings, time between current and previous reading, time since birth and their current medication (Table 19).

4.3.4.2 *Smartphone App*

The smartphone app had the same capabilities as the SMS service, and in addition allowed participants to view a graph of their BP history, their medication adjustment schedule, whether their submitted BP readings were up to date, and their list of reported symptoms. The app could be downloaded from the Google Play Store (Android) or the App Store (Apple iOS), but only users registered on the website by the trial team (sections 4.3.4 and 4.3.4.3) were able to access the app beyond the login page.

4.3.4.3 *Management website*

The telemonitoring system included a management website where participants were registered by a member of the research team following randomisation, which allowed the research team to view participants' BP readings, compliance, adverse events, and create and manage their medication plans (section 4.3.3). Participants could also log in to the website to view their own data.

Participants were registered using their mobile phone number, which also served as their log-in ID for the website and smartphone app. Participants were registered after randomisation, but only activated following hospital discharge, at which point the system allowed submission of BP readings. The rationale for this two-step process was that participants would commence monitoring only after discharge from hospital (to avoid generating potentially conflicting BP readings), and therefore it was important that the system did not 'expect' readings to be submitted (and so send reminders)

before a participant had gone home from hospital after birth. The date of delivery was recorded at registration, and the date of discharge at activation.

The website was also developed and scaled to allow research staff to monitor and manage the clinical information created during the intervention, remotely. To this end the system allowed patients to be divided by NHS trust areas, and the research teams from each area could view a prioritised list of their respective patients. This was designed with future clinical application in mind: allowing similarly stepped access by individual patients' midwives and GPs.

4.3.5 Safety

During the TASMINH2 trial, a simpler unidirectional system allowed BP to be transmitted from the monitor memory, with intervention by the research team limited to checking that medical advice had been sought in the event of a BP reading outside the safety thresholds. However, these patients had a previously established care pathway with their GP having responsibility for their essential hypertension management. Postnatal women with HDP require handover of their care from secondary to primary care, and the audit work (Chapter 3) suggested this was currently inconsistent. Together with the more acute nature of HDP and the risk of severe complications, including stroke and eclampsia, which persists postpartum (section 1.7.2); this meant that it was essential that the SNAP-HT telemonitoring system provided a robust means for the trial team to detect problems. Potential concerns were poor compliance with monitoring, very high or low BP readings and participants reporting symptoms. A system of automated alerts was designed to provide the trial team with twice daily updates about these issues.

4.3.5.1 Missed readings

For safety, the system needed to recognise and respond if a participant failed to submit a BP reading for a given period. This was based on the NICE guidance regarding the frequency of BP monitoring postpartum (1). How soon participants needed to be reminded or contacted depended on: how

recently they gave birth; whether they remained on antihypertensive treatment; and what their most recent BP reading was (Table 20).

Table 20: Timing of reminder messages for missed readings

Treatment status	Day after birth	Most recent accepted blood pressure reading *	Reminder message sent to participant [†]	Research team to contact participant [‡]
ON or OFF (daily readings)	Any stage	Red, orange or purple	24 ⁺¹² (36) hours	48 ⁺² (50) hours
	≤day 14	Blue, green or yellow	48 ⁺² (50) hours	72 hours
	>day 14	Blue, green or yellow	96 ⁺² (98) hours	120 hours
OFF (weekly readings) [§]	>day 14	Any	2 weeks	3 weeks

4.3.5.2 Symptom reporting

Participants were able to report any new symptoms that they experienced via the SMS service or the app. Symptoms were reported as free text. All symptoms, together with BP values outside safety ranges were automatically flagged on the system:

- SBP ≥160mmHg OR DBP ≥110mmHg at any stage in the trial (red);
- SBP <90mmHg AND diastolic <50mmHg whilst on antihypertensive treatment.

Patients were instructed to seek medical attention as they normally would, as although the research team were prompted to contact them within 24 hours of receiving notification of an adverse event, this was not necessarily sufficiently timely depending on the reported symptoms. Adverse events were shown on the management website and sent by summary email (section 4.3.5.3). The system continued to flag a participant with an adverse event until a doctor or midwife explicitly reported that the issue had been resolved.

* See Table 17 and Table 18 for blood pressure values corresponding to these colours

[†] Time interval from previous blood pressure reading at which reminder message sent to participant

[‡] Time interval from previous blood pressure reading at which research team alerted of need to contact participant

[§] Participants move to weekly readings once they are off antihypertensive treatment and have submitted five consecutive green blood pressure readings (<140mmHg systolic and <90mmHg diastolic)

4.3.5.3 Email alerts

The central research team received a twice-daily email to inform them of the following information, and prompting them to contact a participant:

- [1] Participants with overdue readings (as per Table 20);
- [2] Adverse events – either submitted by a participant, or automatically generated (section 4.3.5.2);
- [3] Participants who submitted an orange reading (and so had been advised to seek review by their direct care team, who may have altered their medication);
- [4] Participants who reported inconsistent medication.

In the case of annual leave or absence of the person in charge of reviewing the ‘adverse events’ list and participant compliance (the CI), the system enabled temporary assignment of administration rights to another user.

4.3.6 System testing

For participants’ safety the algorithm and telemonitoring system were rigorously tested to ensure they could deal with a wide range of clinical scenarios. To achieve this a set of seven virtual patients, each with six weeks of BP readings, was constructed to cover a spectrum of different combinations of normal and abnormal BP readings, poor compliance or multiple, additional readings, complex medication adjustment schedules and adverse event reporting (example in Table 21).

The systems were tested in real time. Any issues identified were fixed during the testing period, and tests repeated to ensure that the problem had been solved. The SMS, mobile-app and CTU web-application were tested using the same set of virtual patients to ensure there was complete consistency across the different systems. At the end of the testing period for each system the trial team and technology developers met to discuss the results and ensure all issues had been adequately addressed.

Table 21: Example of a virtual testing patient

Treatment plan 'A'				
A0	Labetalol 200mg QDS, captopril 25mg BD			
A1	Labetalol 200mg BD, captopril 25mg BD			
A2	Labetalol 100mg BD, captopril 25mg BD			
A3	Captopril 25mg BD			
A4	Captopril 12.5mg BD			
A5	STOP			
Treatment plan 'B'				
B0	Labetalol 400mg QDS, captopril 25mg BD			
B1	Labetalol 200mg QDS, captopril 25mg BD			
B2	Labetalol 200mg BD, captopril 25mg BD			
B3	Labetalol 100mg BD, captopril 25mg BD			
B4	Captopril 25mg BD			
B5	Captopril 12.5mg BD			
B6	STOP			
WEEK 1		WEEK 2		WEEK 3
Mon (day 6)	151/98 • 149/97mmHg	Mon	132/90	Mon 132/87 Med check
Tue	154/96 • † No change	Tue	128/82	Tue
Wed	💡	Wed	127/78	Wed 129/78
Thu	164/102 • 159/112 ‡ Increase by Obstetrics (B0)	Thu	126/84	Thu 151/98 • 137/91
Fri	142/93	Fri	125/79 AE (bleeding)	Fri 135/90
Sat	139/89	Sat	126/77*(B1)	Sat 128/82
Sun	134/92	Sun	134/91	Sun 127/78
WEEK 4		WEEK 5		WEEK 6
Mon	124/80	Mon	126/78*(B3)	Mon 144/84
Tue	125/78	Tue	131/82 Med check	Tue 148/102 • 146/97
Wed	124/76*(B2)	Wed		Wed
Thu	135/86 Med check	Thu	126/78	Thu 139/91
Fri	138/91	Fri		Fri 135/79
Sat	132/78	Sat	124/78*(B4)	Sat 129/82
Sun	129/76	Sun	132/82 Med check	Sun 127/79
KEY (items in brackets are not applicable to this virtual patient):				
Day of delivery = day 0; day 14 is shaded lilac				
* indicates when a down titration step should occur (letter in brackets indicates which treatment plan, number in brackets indicates which step)				
• indicates when a participant should be instructed to repeat the reading				
‡ indicates when requires hospital review and possible medication increase				
† indicates when requires GP/MW review and possible medication increase				
(§ indicates when requires GP/MW review and possible medication decrease)				
(X indicates a BP that will be rejected as nonsensical, and a repeat requested)				
(Italics indicates BP readings once a participant is off treatment)				
(£ indicates when a participant should be sent a message telling them to switch to weekly readings				
💡 indicates when a participant should be sent a reminder message (24 hours prior to a flag)				
(🚩 indicates when research team needs to be flagged to contact participant)				
AE indicates report of an adverse event – details in brackets				

4.3.7 Participant and staff training

During the TASMIN trials, enrolled participants were invited to group-training sessions prior to commencing the intervention. This design was not suitable for SNAP-HT, where starting the intervention was time-critical, in relation to a participant's discharge from hospital following birth. Therefore women were trained individually to use the monitor and telemonitoring services, after randomisation, at their baseline visit. In addition, participants were provided with detailed BP monitoring instructions, specifically for use of the Microlife WatchBP® Home, which were developed in line with those developed for previous research studies (118). These were illustrated for ease of use, and included a comprehensive troubleshooting section, based on the monitor's instruction manual (Appendix 9).

To allow both the research team and participants to operate the telemonitoring system, illustrated instruction manuals were developed. These were separate from the trial working instructions (section 4.4.1.6), but were referenced in this document. A manual for participants was developed which included details about how to utilise the SMS service, smartphone app and website (Appendix 10). A manual was developed for the research team, detailing how to use the telemonitoring website, including (Appendix 11):

- Login;
- Registering participants (including details of their current medications);
- Viewing participant details;
- Creating and editing medication plans;
- Resolving overdue readings;
- Resolving reported adverse events;
- Resolving inconsistent medications.

4.4 Trial set-up and management

4.4.1 Protocol

A protocol for a pilot RCT was developed to evaluate the intervention described in section 4.3 (Appendix 12), in line with the template published by Research Services, University of Oxford and in consultation with the TMG (section 4.4.4), with support from an experienced CTU. This is available online (<https://www.phc.ox.ac.uk/research/hypertension/pregnancy/snap-ht-1/snap-ht-protocol-v5-1.pdf>). The study flowchart is shown in Figure 17.

The protocol detailed what patient identifiable information and demographic data would be collected during the study. Deprivation scores using the English Indices of Multiple Deprivation (IMD), 2010 (<https://www.gov.uk/government/statistics/english-indices-of-deprivation-2010>) were calculated online from a participant's postcode using the calculator developed by the National Perinatal Epidemiology Unit (NPEU) (<https://tools.npeu.ox.ac.uk/imd/>).

For further details regarding the contents of the study protocol see section 4.5.2 (Methods).

4.4.1.1 *Patient and public involvement*

Patient and public involvement was critical during the study set-up. Several patients with a history of pre-eclampsia or gestational hypertension were asked to comment in writing on the participant information sheet (section 4.4.1.2.2). They were asked to complete a standardised structured questionnaire with space for free-text comments. This led to the introduction of a summary page at the front of the information sheet (Appendix 13). The same patients were also asked to comment about the consent process (section 4.4.1.2.3). The CI and TMG had considered whether confirmation of consent in writing after birth was necessary, in light of the fact that screening and consent took place during pregnancy, and the intervention only commenced following birth (Figure 17). In general the patients agreed that a two-stage consent process would be beneficial.

To gain an understanding of local mobile telephone usage a brief, anonymous, tick box survey was conducted in antenatal clinic at the different sites. In total 31/31 (100%) of respondents reported owning a mobile telephone, with 30/31 (97%) reporting that their mobile was a smartphone. This supported establishing a study, which required patients to utilise their own mobile telephone, and given the high proportion of women with a smartphone suggested value in developing a smartphone app for use in telemonitoring.

4.4.1.2 Study documents

Alongside development of the study protocol, the patient-facing documents were produced in consultation with the TMG and the CTU (Appendix 13). This section will describe the study advert, participant information sheet, informed consent form, letters to participants' GPs and community midwives and BP monitoring diaries. All documents were individualised for the different recruitment sites (NHS Trust logo and local contact details).

4.4.1.2.1 SNAP-HT advert

A single page advert was developed, which included a statement about the objective of the study, and a list encompassing the inclusion and exclusion criteria. The advert contained contact details for the CI (the author), and was designed for use in clinical areas at all sites to inform both patients and clinical staff about the study.

4.4.1.2.2 SNAP-HT participant information sheet

A participant information sheet was developed to provide participants with more detailed information about the study if they expressed an interest. The structure and content of this was based on a Standard Operating Procedure from the Sponsor (University of Oxford) 'Preparation of participant information sheets and informed consent forms' (283), and published advice from the Health Research Authority (284). After an initial draft was produced, this was amended in line with feedback from patients (section 4.4.1.1).

4.4.1.2.3 SNAP-HT informed consent form

An informed consent form was developed in line with the advice from the Sponsor (University of Oxford) and the Health Research Authority (283, 284). This was produced in two parts: one for the main study, and a second for the two optional sub-studies (Chapters 5 and 6). Participants needed to initial multiple statements regarding provision of information about the study, data collection, sharing, storage and retention and then sign and date each part of the form. The forms were printed on triplicate carbon paper in order that a copy could be given to the participant, a copy inserted into their maternity notes, and a copy retained by the research team: this copy was stored securely with the patient identifiers form (section 4.4.1.3), and separately from all trial data which were stored anonymously under participants' study identification numbers.

Following discussion with the Quality Assurance team at the Primary Care CTU (University of Oxford) and advice from the REC it was decided that a two-stage consent process was unnecessary (sections 4.4.1.1 and 4.4.2.1). Therefore, there was a single consent form, which was signed at the screening visit by both the participant and the researcher. At the baseline visit consent was confirmed, and this was documented in the participant's maternity notes.

4.4.1.2.4 SNAP-HT letters to participants' GPs and midwives

Letters to participants' GPs and midwives were designed for both groups. These detailed a participant's inclusion in the study, their diagnosis and discharge medication, and gave an overview of the implications of their involvement. These were designed so that the majority of the text was fixed, and were pre-signed, with space to write a participant's details, select their diagnosis (gestational hypertension or pre-eclampsia) and document their discharge medications in table format. A copy of the study flowchart (Figure 17) was incorporated into these letters. Contact details for the study team were provided. These letters were sent after birth, following randomisation, prior to hospital discharge.

4.4.1.2.5 SNAP-HT blood pressure monitoring diaries

Participants in the self-management group were provided with a BP monitoring diary for them to record their BP readings in writing, in addition to submitting them via the telemonitoring service, if they wished to do so. This allowed documentation of both readings taken, as well as acknowledgement that the second reading was submitted via the telemonitoring service, and what advice was received. This diary had space for participants to record up to 12 weeks of daily readings, and then weekly readings from week 13 – week 26 (end of follow-up). If participants continued on medication beyond 12 weeks a supplementary diary was provided. The diary also had space for participants to document their medication changes. Participants in the usual care group were provided with a template to document their medication changes, as advised by their GP.

4.4.1.3 Case report forms

The case report forms (CRF) were developed from a data point list derived from the study protocol. These were designed in collaboration with an experienced Clinical Trial Data Manager. One CRF was designed to capture all patient identifiable information listed in the protocol. This form was stored securely in a locked filing cabinet, separately from any clinical data, such that no connection could be made. Access to this data was strictly restricted to appropriate members of the study team (as detailed on the delegation log). This data was only stored in paper format, and was not recorded electronically. Explicit consent (optional) was obtained from participants to retain their contact details in order to contact them about future related research. For participants who declined to consent to this, their identifiable data was destroyed securely within three months of the end of the study.

On all other CRFs participants were identified solely by their study identification number. A unique CRF was designed for each of the seven trial visits. These were designed to capture all the research data as specified in the protocol, with as limited free text as possible. The screening and baseline

forms were piloted (anonymously) from some maternity notes to ensure they were straightforward to use, and gathered the required information in an appropriate format.

4.4.1.4 Trial database

Using the CRFs as a basis, a database to record and store the trial data was designed and tested prospectively. This was designed by an experienced Clinical Trials Programmer, using the software 'OpenClinica', and was tested prior to implementation.

The paper CRFs were collated centrally, and checked by the CI (the author). The trial data were double entered into the database by the data management team within the CTU, as the trial was ongoing, and the CI addressed data queries contemporaneously. The database was locked at the end of the trial, after undergoing a standardised process of data checking and cleaning, which was completed by the author in collaboration with the data management team.

4.4.1.5 Peer review

An outline of the original study idea was submitted for review as part of the NIHR Oxford CLAHRC programme application. The detailed study protocol, written by the CI, was submitted to two independent peer reviewers for their comments in August 2014. Their comments were favourable, and following this the protocol, together with the study documents (section 4.4.1.2), was subjected to internal quality assessment by the CTU (section 4.4.2.1).

4.4.1.6 Working instructions and study training

To facilitate the day-to-day running of the trial across the different sites a comprehensive set of stepwise, illustrated working instructions were developed to address all aspects of the main study and the sub-study. A PowerPoint presentation was put together to summarise these instructions, and to provide the basis for the research team training at each site. This was conducted at the site initiation visits, and the research teams were required to sign to say they had attended the training, received a copy of the working instructions and read the current trial protocol.

4.4.2 Clinical Trials Unit (CTU)

4.4.2.1 *Quality assurance*

Before submitting the study protocol and patient-facing documents to the Sponsor for review, they were subject to internal quality assurance, provided by the Primary Care CTU. Several alterations were made because of this process:

- Consent process: after consultation with the CTU and seeking advice from the Research Ethics Committee (REC), the decision was made to take written consent for participants only once (at the screening visit, during pregnancy). The reason for this decision was that there was a concern that errors would be more likely to be introduced by the proposed two-stage consent process;
- It was clarified that all patient identifiable information would be stored centrally within the Nuffield Department of Primary Care Health Sciences, University of Oxford (including informed consent forms). A clause stating this was included in the informed consent form;
- Feasibility outcomes: explicit descriptions of these outcome measures were included;
- Serious adverse events (SAEs): a list of expected SAEs – both related and unrelated to BP management – was added;
- A section detailing the University's policy on lone working was added, in view of the fact that the study follow-up involved visiting participants at home.

4.4.2.2 *Risk assessment*

A standardised risk assessment form from the CTU was completed, and then discussed at a meeting involving the following: CI, Trial Data Manager, Clinical Trials Programmer, Trial Statistician and Quality Assurance Manager. Following this meeting, the risk assessment form was finalised and signed by the Quality Assurance Manager, the CI and the CTU Director.

The first section of this form is dedicated to particular risks associated with an intervention. It was decided that the risks associated with the intervention were comparable to the risk of standard medical care, as participants with a high BP would still follow standard clinical management. Furthermore the frequency of HBPM in the intervention group was in line with guidance from NICE. In terms of medication down-titration, the same BP thresholds would be employed as are recommended by NICE for standard care and therefore this should not increase risk.

Specific risks related to the trial design were identified, such that plans for risk minimisation and monitoring could be put in place. Specific areas of concern included: consent, personal data storage, randomisation, intervention, resources, follow-up, data, lone working and trial governance.

This risk assessment formed the basis for the level of monitoring required by the study. All recruiting sites received a site initiation visit and closure visit as a minimum, and additional targeted site visits as required. As the intervention was novel in this population, it was decided that although this was a pilot study, a formal independent DMEC should be convened (section 4.4.5). However, as the study was a pilot, no separate Trial Steering Committee was required. A TMG had been formed following the relevant CTU SOP (section 4.4.4).

4.4.2.3 Statistical analysis plan

As stated in the ethics application the statistical analysis plan (Appendix 14) was completed and signed off before receipt of any trial data. The statistical analysis plan was drafted by the CI, in collaboration with the Trial Management Group and the Trial Statistician, and was reviewed and approved by the DMEC. For further details, see section 4.5.2.8.

4.4.3 Sponsor

Following internal approval from the CTU, the study protocol and associated documentation were submitted, together with funding and statistical support letters, the peer review forms and curricula vitae for the CI and Principal Investigators, to the study Sponsor (University of Oxford) in August

2014. After review by the Sponsor's representative the following adjustments were made, prior to their approval being granted:

- Further detail was added to the protocol regarding the BP monitor used during the study, including the make, model, validation details and who owns the monitors themselves;
- The visit numbers were amended such that the screening visit became visit 1, and the baseline visit therefore became visit 2 (previously this was referred to as visit 1);
- The consent process was clarified further, regarding detailing ongoing consent at the baseline visit in writing in the maternity notes;
- Sample handling for the vascular risk sub-study: further detail was added regarding gifting of samples, and transfer to a tissue bank at the end of the study;
- The patient information sheet was altered to emphasise that this was a pilot (or feasibility) study, with a view to conducting a larger scale research project in the future;
- The protocol was amended to include a section detailing criteria for success of the feasibility study.

The University of Oxford has a specialist insurance policy in place, which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, Lloyd's of London). NHS indemnity would operate in respect of any clinical treatment that was provided.

4.4.4 Trial Management Group (TMG)

A TMG was established to provide overall supervision for the trial on behalf of the Trial Sponsor and Trial Funder and to support the CI in the day-to-day running of the trial. The TMG focused on the progress of the trial, adherence to the protocol and patient safety. The TMG was to assist the CI in providing evidence to support any requests for extensions, indicating that all practicable steps had been taken to achieve targets.

The TMG was comprised of the CI and members of her supervisory team, including an Obstetric Physician, a Cardiologist with a research interest in hypertension in pregnancy, a GP with a research background in self-management in essential hypertension (CI for the TASMIN trials) and a senior researcher (CI for the BuMP study – section 4.3).

During the course of the trial, the TMG met on an approximately monthly basis. A written report was prepared in advance of each meeting by the CI, and following the meeting, a set of minutes was completed including an action plan.

4.4.5 Data Monitoring and Ethics Committee (DMEC)

The roles and responsibility of the DMEC were set out in line with those detailed in the Damocles Study Group Charter for clinical trial data monitoring committees (285). The DMEC's overall responsibility was to safeguard the interests of trial participants, and to assist and advise investigators and the TMG in order to protect the validity and credibility of the trial. The DMEC received and reviewed information (on an agreed six-monthly interim basis) on the progress and accruing data of the trial and gave advice on the conduct of the trial to the TMG. The DMEC met in February 2015 prior to commencement of the study, in November 2015 (6-months after recruitment of the first participant) and finally in March 2016 after completion of trial follow-up and the main statistical analysis.

The DMEC conducted interim reviews of the trial's progress and were provided with data for recruitment, allocation balance, data quality and completeness, follow-up, and assessment of adverse events. They monitored the implementation of trial protocols, and provided advice regarding proposed protocol modifications. They reviewed the statistical analysis plan (section 4.4.2.3) for the trial, and suggested additional data analyses where necessary. The DMEC also assessed the impact and relevance of external evidence, and were to decide whether trial follow-up should be stopped earlier (no formal stopping rules were enforced). The DMEC was to inform the CI if in their view:

- [1] EITHER: The trial results were likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that on balance one trial arm is clearly indicated or contraindicated for all participants or a particular category of participants, and there was a reasonable expectation that this new evidence would materially influence patient management;
- [2] OR: It became clear that no clear outcome would be obtained.

4.4.6 Research Ethics Committee (REC) approval

Following approval from the Sponsor (23 September 2014), the study protocol was submitted, together with the patient-facing information (section 4.4.1.2) and application form for consideration by the REC – NRES Committee South Central, Oxford C – via the Integrated Research Application System (IRAS) on 29 September 2014. An ethics committee meeting was attended on 31 October 2014, and a provisional opinion from the REC was received on 6 November 2014. After minor alterations, ethical approval for the study was granted on 19 November 2014.

4.4.6.1 Substantial amendments

Two substantial amendments were submitted to and approved by the REC. The first was submitted on 20 January 2015, and approved by the REC on 4 February 2015. In this amendment, the protocol and participant information sheet were amended to include the weighing of participants at baseline, and at the three and six month follow-up visits. During the research and development approval process (section 4.4.7) the Clinical Research Network requested a series of changes to the protocol and patient facing information. These were incorporated into this substantial amendment: The informed consent form and participant information sheet were updated to explicitly state that anonymised direct quotations would be used when reporting the results of the patient experience qualitative sub-study. The GP letters were updated to remove the statement about service support costs, as costs would only be paid if study visits were held at GPs surgeries and rooms hired.

Additionally the BP monitoring diaries and medication changes documents were submitted to the REC (as these had been omitted from the original submission).

The second substantial amendment was submitted on 9 June 2015, adjusting the time windows for several visits in the protocol, including allowing the first of the two vascular risk sub-study visits to take place at either the baseline visit, or 10-day follow-up. In the protocol the definition of SAEs was further clarified, and the analysis of outcome measures section was updated, such that the minimum proportion of participants contributed by one site was changed from 10% to 5%. The reason for this change was that Banbury was counted as a separate area from Oxford in terms of recruitment figures (although they are part of the same NHS Trust). Banbury has a much smaller number of births (approximately 1500 per year) than the other areas (5500-7000 per year), and the majority of their high risk cases are transferred to Oxford. This was approved on 22 June 2015.

4.4.6.2 *Non-substantial amendments*

Three non-substantial amendments were submitted to and approved by the REC during the study. The first (16 February 2015) was to update the version number and date on the informed consent form as these were incorrect. The second (20 May 2015) was to add two research midwives to the research team at one site (Oxford University Hospitals NHS Foundation Trust). The third was to clarify the title and role of the DMEC. This amendment was submitted on 7 June 2016 and approved by the REC on 24 June 2016. They classified this as a Category C amendment: an amendment that has no implications that require management or oversight by the participating NHS organisations.

4.4.7 Research and Development approval

In order to allow completion of the technology development and testing (sections 4.3.4 and 4.3.6) the global research and development application was deliberately delayed after receiving REC approval. This was submitted via IRAS on 6 January 2015, and was processed through the Coordinated System for Permissions by the Thames Valley NIHR Clinical Research Network. They

granted approval on 16 February 2015, after the substantial amendment described in section 4.4.6.1 was approved by the REC.

4.4.7.1 *Contracts*

Following global research and development approval, the participating site agreements for the four NHS trusts were signed. For the Oxford University Hospitals NHS Foundation Trust this included a services agreement as an appendix, to include the projected costs for laboratory analysis of the blood samples taken during the vascular risk sub-study.

4.4.7.2 *Trust Management Approval*

Recruitment for the study took place across four NHS hospital trusts. Study follow-up took place in the community, and in primary care, so approvals were also sought from the Clinical Commissioning Groups (formerly Primary Care Trusts) and the community health trusts. The site-specific information forms were completed through IRAS, and submitted after agreement with each site (from March to July 2015). Trust Management Approvals were granted prior to recruitment commencement at each site (Table 23).

4.4.7.3 *Letters of access*

The CI and research midwives for the study all held a clinical contract with one of the NHS hospital trusts participating in the research, so permission to conduct research across the other sites was granted to each individual in the form of letters of access. These applications were made during the process of gaining local research and development approvals.

4.4.8 *ClinicalTrials.gov registration*

In line with the Department of Health's Research Governance Framework for Health and Social Care (286), and Article 35 of the World Medical Association Declaration of Helsinki (2013) (287) the trial was prospectively registered on a publicly accessible database

(<https://clinicaltrials.gov/ct2/show/NCT02333240>). This occurred before recruitment of the first subject. This registration was updated throughout the trial, and following trial completion.

4.4.9 NIHR Portfolio adoption

A portfolio adoption form was omitted during completion of the original IRAS application. Therefore, an application was submitted retrospectively, and the study was accepted for adoption onto the NIHR portfolio on 1 October 2015. During the course of the study, monthly recruitment figures were uploaded onto the Central Portfolio Management System.

4.5 Study

4.5.1 Objectives

The main objective of this pilot study was to assess the feasibility of testing the self-management intervention for postnatal antihypertensive treatment (section 4.3) in a multicentre open-label RCT. In particular, the study processes, required resources, trial management and scientific measures were evaluated (179, 180). The recruitment and retention rates, acceptability of the intervention were measured, and the randomisation procedure and integrity of the protocol were tested. The proposed questionnaires and time to conduct study procedures were explored. CRFs, the trial database and centre willingness and capacity were tested. Estimates of the treatment effect were made with a view to facilitating selection of the most appropriate primary outcome measure for a large-scale trial, and the safety of the proposed intervention was reported. This randomised pilot trial is reported in line with the CONSORT 2010 statement: extension to randomised pilot and feasibility trials (Appendix 15) (288).

4.5.2 Methods

4.5.2.1 Study oversight

The SNAP-HT pilot study was registered with ClinicalTrials.gov (NCT02333240). The trial was approved by the National Research Ethics Service: NRES Committee South Central, Oxford C – 14/SC/1316 (section 4.4.6), and the Research and Development service at each hospital (section 4.4.7). Study oversight and monitoring were provided by the TMG and the DMEC (sections 4.4.4 and 4.4.5).

4.5.2.2 Study participants

The participants in the SNAP-HT pilot study were recruited from five NHS hospital sites (four NHS trusts) in the United Kingdom. Women were eligible if they were aged 18 years or over with a diagnosis of either gestational hypertension or pre-eclampsia, requiring antihypertensive treatment,

and were recruited prior to discharge from hospital after birth, provided they had capacity to consent to participation in research.

Women under the age of 18 years were excluded as it was not considered that in this pilot study additional benefit would be derived from conducting the research in minors (as per guidance from the General Medical Council (289)), especially due to the lower incidence of HDP among younger women. Women were excluded from the trial if they had poor English language skills, as the resources to translate study materials were lacking at this pilot study stage.

Women who were prescribed more than three different antihypertensive medications were ineligible. The rationale for this decision was two-fold: this was the first experience with pre-determined medication adjustment schedules, so it was felt that more than three different medications would result in an excessive level of complexity; clinical experience suggests that women requiring this level of antihypertensive treatment often have a particularly turbulent clinical course, and may be found to have secondary hypertension.

Women with a definite diagnosis of hypertension which predated pregnancy were excluded. The intention of the intervention was to down-titrate and ultimately stop antihypertensive treatment postpartum (where appropriate), and women entering pregnancy with definitive chronic hypertension, on treatment, will be managed differently after birth: they will usually be returned to their pre-pregnancy antihypertensive regime. Women who had a speculative diagnosis of essential hypertension made during pregnancy (based on a high-normal booking BP, or a new diagnosis of hypertension in the second trimester) were not excluded.

4.5.2.3 Study procedures

The sequence of study procedures is outlined in Figure 17. Participants were approached during pregnancy, and provided with written information to consider. If they wished to take part they then

gave written informed consent at the screening visit before baseline data was collected. Consent was confirmed at all subsequent visits.

After birth participants were seen for a baseline visit prior to hospital discharge. At this visit consent and eligibility were confirmed, and further medical details were collected, particularly with regard to details of the birth and hypertensive diagnosis. They had their BP measured six times, at one minute intervals, using a validated, automated monitor (Microlife WatchBP Home®) (128). Their current antihypertensive medication(s), concomitant medication(s) and side effects were recorded.

Women from both groups attended five follow-up visits over six months after delivery: ten days (visit 1), four weeks (visit 2), six weeks (visit 3), three months (visit 4) and six months (visit 5) (Figure 17). The majority of these visits took place in participants' homes. At each visit BP was measured in the same way as described for the baseline visit, and the following information was recorded: current antihypertensive medication and changes since previous visit; side effects; SAEs; concomitant medication(s).

In addition to the subgroup of participants undertaking the audio-recorded qualitative interviews (Chapter 5), all participants completed a validated quality of life questionnaire (EQ-5D-5L™) (290) at screening, six weeks and six months.

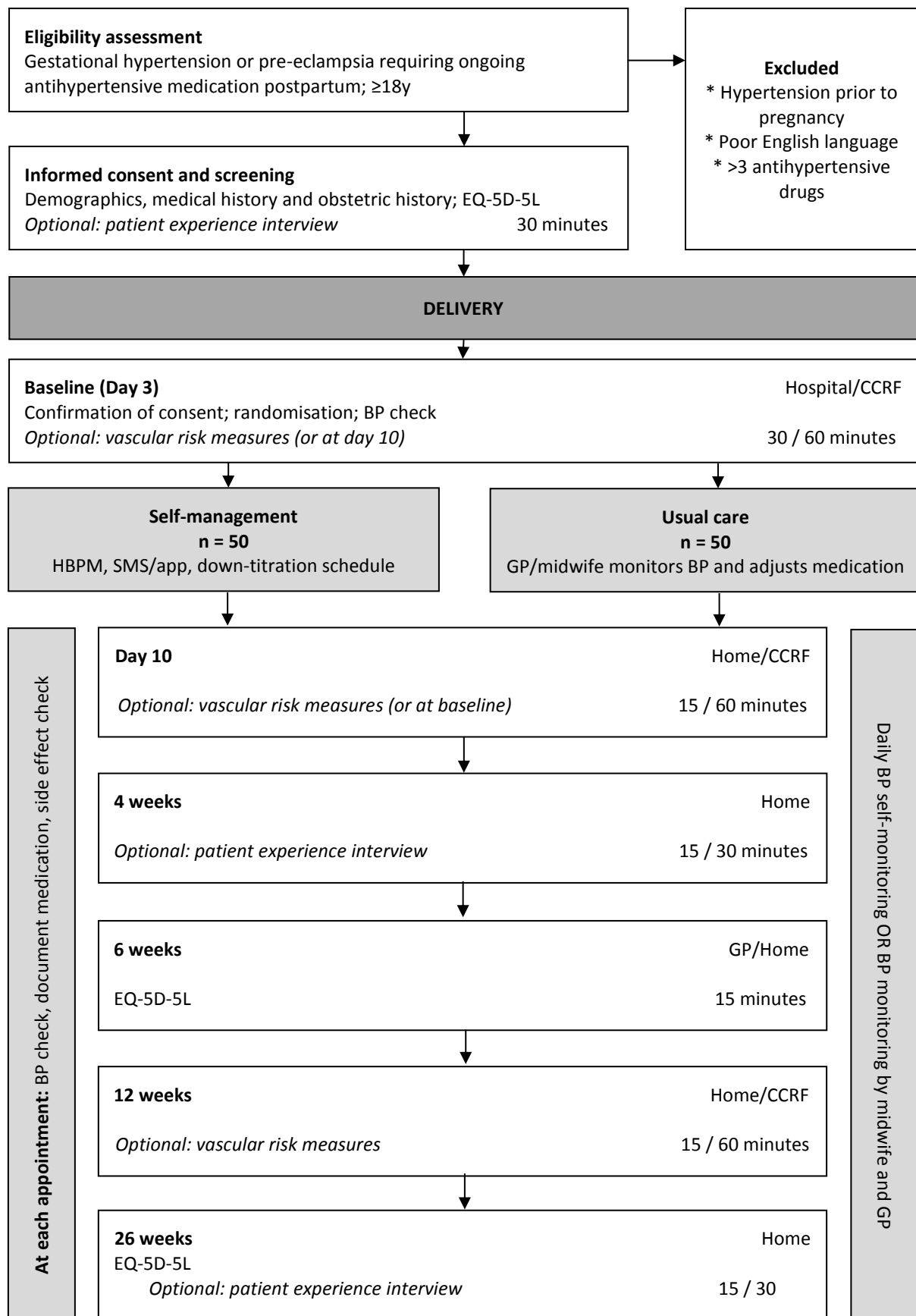


Figure 17: SNAP-HT Study Flowchart

4.5.2.4 Randomisation

Randomisation took place after birth. Women were excluded at this stage if they withdrew consent, or lost capacity to consent, or if they became ineligible due to cessation of antihypertensive treatment (Figure 19). Women were randomly allocated after birth in a 1:1 ratio to self-management of antihypertensive treatment, or to usual postnatal care, stratified by recruitment centre. The trial was open-label.

A secure web-based open randomisation system was developed by the Primary Care CTU (Sortition: <https://ctu1.phc.ox.ac.uk/randomise/login>). The CI (the author), the TMG and the trial statistician agreed the specification. The randomisation was stratified by study site, and women were block randomised 1:1 to self-management or usual care (block sizes 2 or 4, with a sequence length of 40). This was to reduce the chance of any investigator guessing the block size and thus the likely order of randomisation. Participants were randomised using their study identification number.

4.5.2.5 Study intervention

Self-management (section 4.3) commenced following discharge from hospital after birth, and entailed daily HBPM, whilst on antihypertensive treatment, with submission of BP readings via a mobile phone-based telemonitoring system, which provided automatic feedback and incorporated an individualised medication adjustment schedule (section 4.3.3). The telemonitoring system collated submitted BP data centrally (section 4.3.4.3), and at the end of the study period the data from the home BP monitors was downloaded and stored. Women randomised to usual care had their BP monitored by their community midwife, and their antihypertensive medication adjusted by their GP.

4.5.2.6 Recruitment plan

The intention was to recruit 100 participants across the four NHS trusts (Figure 18) over a planned nine month recruitment period.

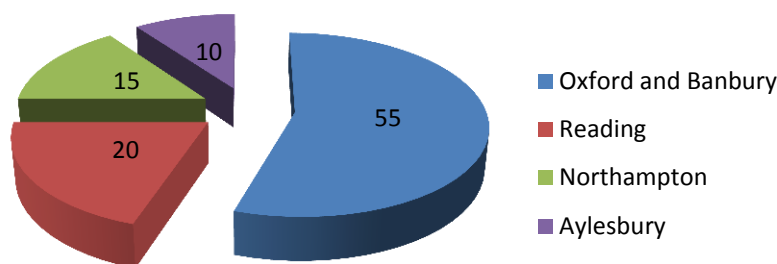


Figure 18: Recruitment targets

4.5.2.7 Outcome measures

The primary outcome was feasibility: recruitment, retention and compliance rates. These were measured by completion of screening and recruitment logs throughout the trial at all sites, and through completion of a withdrawal form when participants withdrew or were lost to follow-up.

Secondary outcomes included several different measures of BP control: mean SBP, DBP and MAP were compared at different follow-up time points, and across the follow-up time period. Mean BP readings were classified as being inside or outside target ranges, and also inside or outside safety ranges. Postnatal readmission rates, safety data and side effects from antihypertensive medication were reported. The study utilised the EQ-5D-5L™ quality of life assessment (registered for use via the EuroQol website (<http://www.euroqol.org/register-to-use-eq-5d.html>)). This tool was amalgamated into the CRFs (section 4.4.1.3), and compared between groups and across the study period.

Exploratory outcomes included compliance with, and accuracy of HBPM in the intervention group. These were calculated using data from the telemonitoring service, and downloaded from each participant's home BP monitor. In essential hypertension, a home BP of 135/85mmHg is considered equivalent to an office measurement of 140/90mmHg (127). Limited evidence exists regarding whether different BP thresholds should be used for HBPM and office BP monitoring in pregnancy. Therefore variation between a participant's trial follow-up BP readings (equivalent to 'office' BP measurement) and home BP readings was explored across study follow-up.

4.5.2.8 Statistical analysis

See also section 4.4.2.3 and Appendix 14.

4.5.2.8.1 Sample size

A formal sample size calculation was not performed for this pilot study. The choice of sample size was based on published recommendations suggesting that a sample size of at least 70 is required to estimating the standard deviation of a normally distributed variable (291). They also discuss the potential for a larger sample size (60 per group) being advantageous when analysing the recruitment parameters for a trial but acknowledge the need to balance maximising the precision of a pilot study with minimising the size of an external pilot study to limit impact on time and resources (291). The Medical Research Council suggest a larger sample size may be necessary when evaluating a complex intervention in a pilot study (166).

The target sample size chosen was 100 women (i.e. 50 women randomised to each arm). This was based on the projected population size from which to recruit over a nine-month period. A two-month coded database search, and subsequent medical record review at the main recruitment centre (Oxford University Hospitals NHS Trust), estimated that 25 patients per month across the two sites (Oxford and Banbury) had gestational hypertension or pre-eclampsia and required antihypertensive medication after postnatal hospital discharge (section 3.5). Given the relative sizes of the different centres, it was calculated that across the sites approximately 60 women per month might be eligible for the study (540 in nine months) giving a required recruitment rate of approximately 20%.

4.5.2.8.2 Primary analysis

The analysis was carried out based on intention-to-treat. Analyses were conducted on all patients randomised, for whom any follow-up data was available, were primarily descriptive and did not include any hypothesis testing. Continuous variables were summarised as means with standard

deviations (or medians with interquartile ranges if skewed), and categorical variables as counts and percentages. Differences between groups were reported with 95% confidence intervals only and did not include significance tests with P-values.

The MAP for each BP measurement was calculated from the recorded SBP and DBP readings using the following formula: $MAP = [(2 \times DBP) + SBP]/3$. To inform a future main trial, the differences in mean SBP, DBP and MAP between groups were estimated using a mixed effects regression model. The model included the outcome with randomised group, time and an interaction between time and randomised group as fixed effects, adjusting for recruitment site and BP at baseline, fitted as fixed effects with an unstructured covariance pattern. The differences in the adjusted means between the treatment groups at each time point were calculated.

For the combined mean BP across follow-up, a linear regression model was fitted with treatment group as the independent variable, adjusting for recruitment centre and BP at baseline. Follow-up BP readings were classified as inside or outside a target range, and inside or outside safety thresholds. These binary outcomes were compared between groups at each time point utilising logistic regression models, with randomised group and recruitment centre fitted as covariates.

4.5.2.8.3 Sensitivity analyses

For all BP outcome measures, two mean readings, at each follow-up visit, were calculated from the data: the mean of the second and third readings (two readings); and the mean of the second to sixth readings (five readings). The first reading was always discarded to reduce the 'white coat' effect (section 1.9.1). It was anticipated that the intervention group could become more habituated to BP monitoring, thereby dampening their 'white coat' effect relative to the control group. Sensitivity analyses for all BP outcomes using the mean of the second to sixth readings attempted to reduce the potential bias this habituation may introduce.

4.5.2.8.4 Exploratory analyses

There were two datasets for HBPM from each participant in the intervention group: that from the readings submitted via the telemonitoring service; and that downloaded from the BP monitor memories, in which 200 readings could be stored. These were utilised to assess participant accuracy and adherence to the HBPM schedule. The percentage of measurements reported both incorrectly (any difference) and incorrectly with clinical significance (at a different BP threshold (section 4.3.2)), were calculated to evaluate the accuracy with which participants transcribe and report their BP readings, and distinguish between a minor transcription error and a clinically significant discrepancy.

To explore whether these data provide evidence for a white coat effect (section 1.9.1) in the population with HDP, the research follow-up BP readings (or 'office' BP readings) were compared with the home BP readings downloaded from a participant's monitor. The means of the second and third 'office' reading were used, and compared with the closest (in time) home reading, and also the mean of the closest two home readings. Paired two-sample t-tests were used for these analyses, and raw mean differences reported with 95% confidence intervals.

4.5.3 Results

4.5.3.1 Study participants

188 women were approached between April 1, 2015 and April 30, 2016. 153 were eligible for inclusion: 91/153 (59%) consented to be randomised. 45 were assigned to self-management, and 46 to usual care (Figure 19). 9/91 (10%) withdrew from the study: five from the self-management group, and four from the usual care group. 82/91 (90%) completed follow-up. The baseline characteristics were similar in the two study groups (Table 22), although the mean SBP, DBP and MAP at baseline were slightly higher in the intervention group. Figure 20 and Figure 21 show the geographical distribution of all included participants.

Table 22: Baseline characteristics (n=91)

	Intervention (I) (n = 45)	Control (C) (n = 46)
Mean age (SD) / years	31.7 (5.3)	31.7 (5.3)
Mean BMI (SD) / kg/m²	29.0 (7.5)	28.0 (8.3)
Parity (frequency (%))		
0	32 (71%)	31 (67%)
1	9 (20%)	11 (24%)
2	2 (4%)	2 (4%)
≥3	2 (4%)	2 (4%)
Ethnicity (frequency (%))		
White (British)	38 (84%)	37 (80%)
White (other)	3 (7%)	6 (13%)
Black	1 (2%)	1 (2%)
Asian	3 (7%)	2 (4%)
IMD quintile (frequency (%))		
1 st	16 (36%)	22 (48%)
2 nd	9 (20%)	7 (15%)
3 rd	14 (31%)	9 (20%)
4 th	4 (9%)	7 (15%)
5 th	2 (4%)	1 (2%)
Diagnosis (frequency (%))		
Gestational hypertension	20 (44%)	22 (48%)
Pre-eclampsia	25 (56%)	24 (52%)
Median PCR (IQR) (if pre-eclampsia) / mg/mmol	109.2 (55 to 152.9)	55.4 (41.4 to 114.5)
Median gestation at diagnosis (IQR) / weeks	35.9 (31.9 to 37.7)	34.7 (31.7 to 36.9)
Median gestation at delivery (IQR) / weeks	37.6 (36.2 to 39.2)	37.2 (36.3 to 39.1)
Median duration of AN AHT treatment (IQR) / days	10 (4 to 19)	9 (5 to 22)
Median amount of AHT treatment at baseline visit (IQR) (WHO defined daily dose)	1 (0.7 to 1.5)	1 (0.7 to 1.7)
Mean SBP/DBP at booking visit (SD) / mmHg	119.2 / 72.7 (14.1 / 9.3)	116.8 / 73.0 (12.6 / 9.4)**
Mean SBP/DBP (readings 2+3) at baseline^{††} visit (SD) / mmHg	135.2 / 87.1 (15.5 / 9.2)	130.8 / 85.4 (13.0 / 10.5)
Mean MAP (readings 2+3) at baseline[†] visit (SD) / mmHg	103.1 (10.6)	100.6 (10.7)

Abbreviations: AHT = antihypertensive; AN = antenatal; BMI = body mass index; C = control; DBP = diastolic blood pressure; I = intervention; IMD = Index of multiple deprivation; IQR = interquartile range; MAP = mean arterial pressure; PCR = protein:creatinine ratio; SBP = systolic blood pressure; SD = standard deviation

** n = 44 as missing data for 2 participants

†† The baseline visit is visit 2, and takes place day 1 – 6 after birth

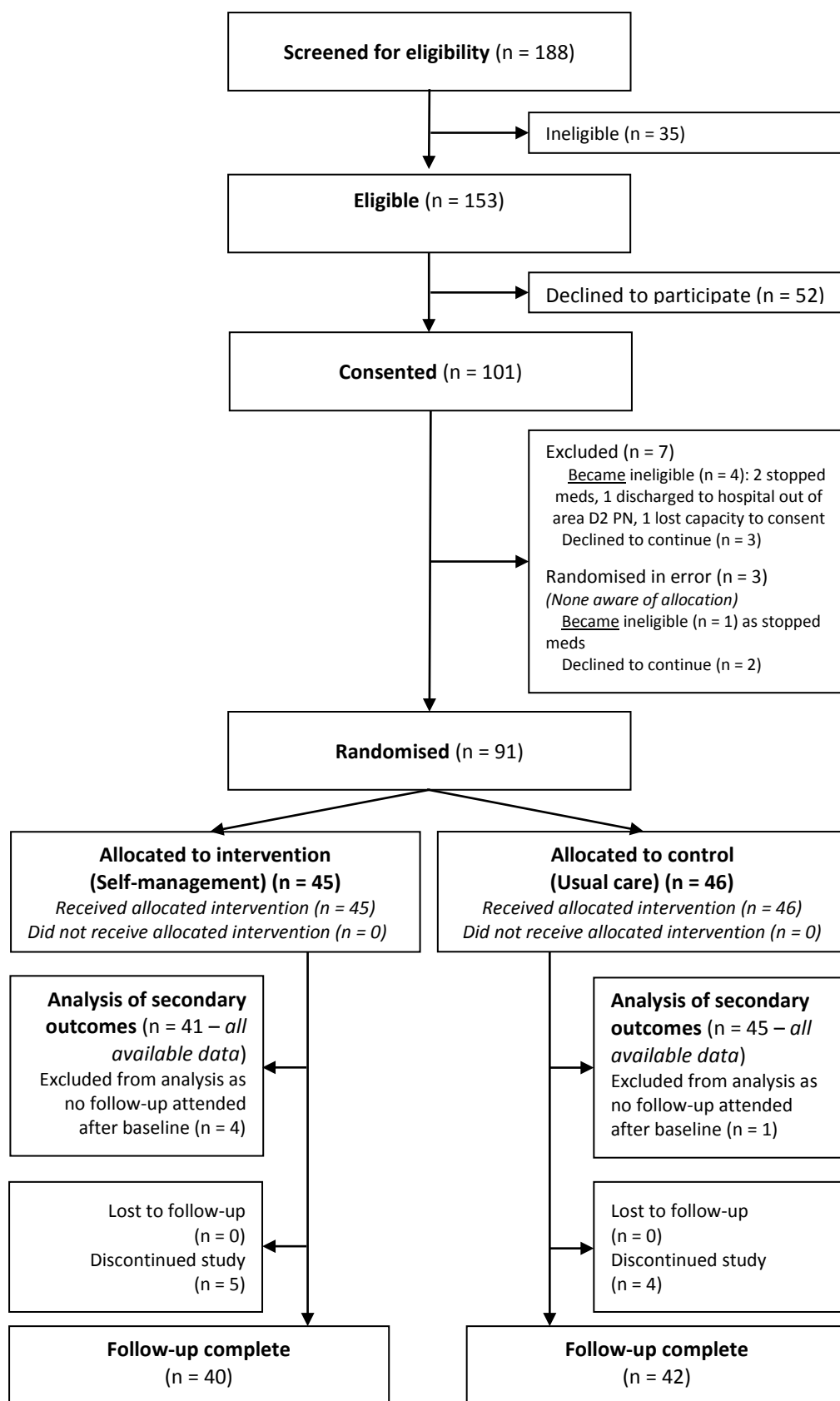
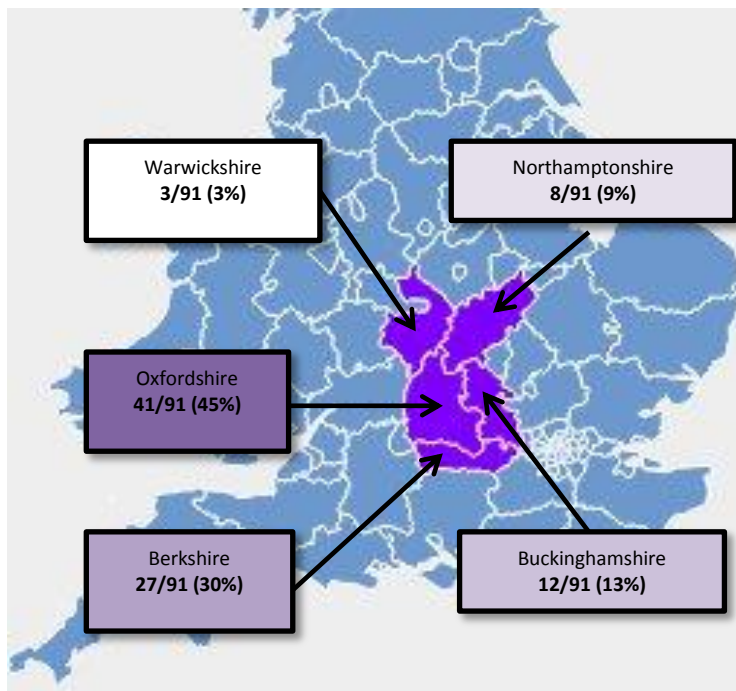
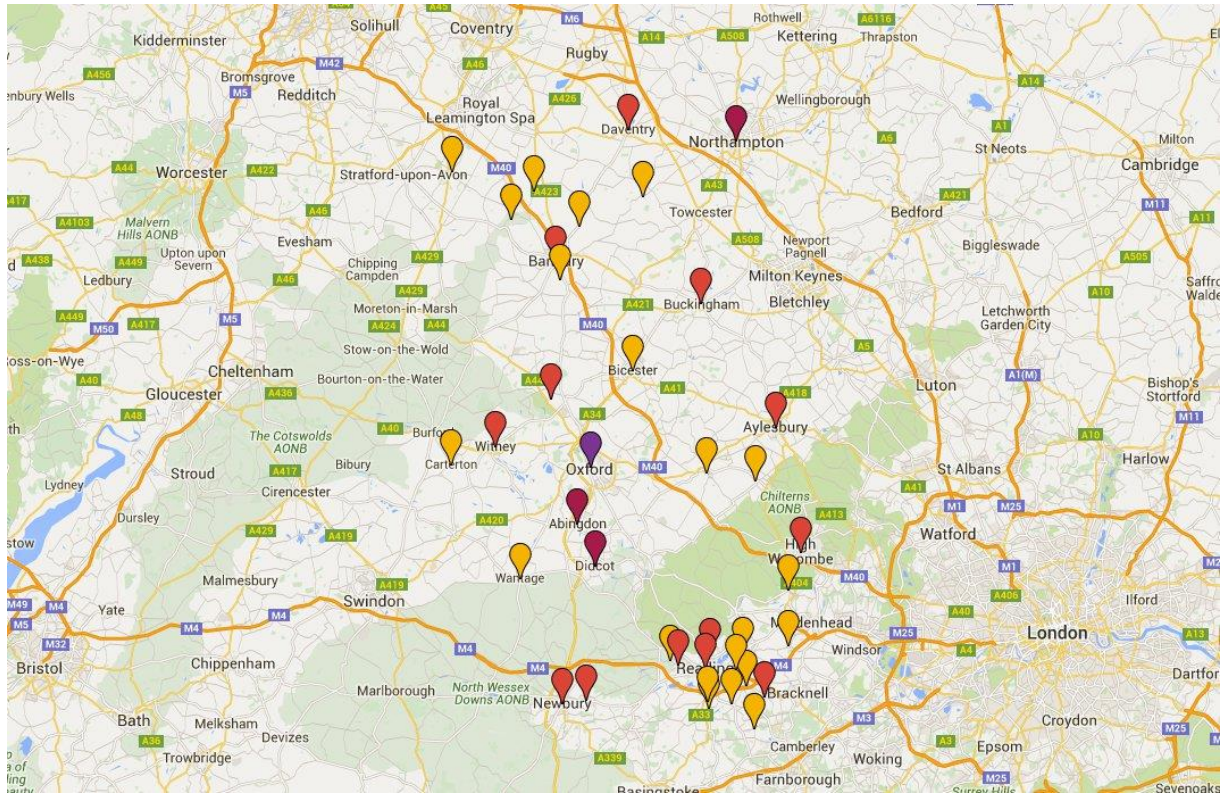


Figure 19: Consort flowchart (enrolment, randomisation, follow-up and analysis)



^{##} KEY: Yellow = 1 participant; orange = 2-4 participants; pink = 5 – 10 participants; purple = >10 participants

4.5.3.1.1 Recruitment progress

Recruitment periods are detailed in Table 23. The initial planned recruitment period of 9-months was extended in order to achieve the recruitment target. The longest actual recruitment period was 13-months. Adjusted recruitment targets and rates across all sites are shown in Figure 22. The overall recruitment rates are divided by recruitment site in Table 24.

Table 23: Recruitment periods

Site	Local Trust Management Approval	Recruitment start date	First participant recruited	Recruitment end date
Oxford and Banbury	16/04/2015	20/04/2015	06/05/2015	30/04/2016
Reading	31/03/2015	01/04/2015	12/05/2015	30/04/2016
Northampton	07/04/2015	29/04/2015	01/05/2015	31/03/2016
Aylesbury	09/07/2015	15/07/2015	30/07/2015	30/04/2016

Table 24: Recruitment rates at each site

Site	Target	Approached	Consented	Consent rate
Oxford and Banbury	55	90	53	59%
Reading	20	64	28	44%
Northampton	15	16	8	50%
Aylesbury	10	18	12	67%
TOTAL	100	188	101	54%

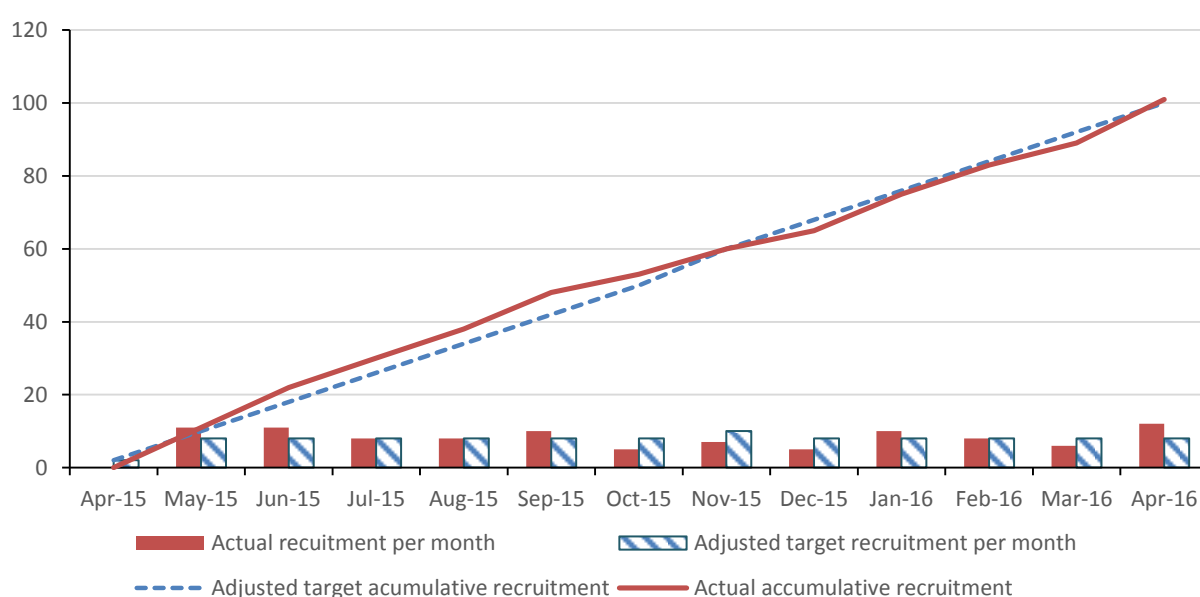


Figure 22: Adjusted recruitment targets and rates

4.5.3.1.2 Recruitment based on eligibility

Table 25: Potential participants not enrolled (declined versus ineligible)

Site	Not enrolled n	Declined n (% total not enrolled)	Ineligible n (% total not enrolled)
Oxford and Banbury	37	27 (73%)	10 (17%)
Reading	36	18 (50%)	18 (50%)
Northampton	8	6 (75%)	2 (25%)
Aylesbury	6	1 (17%)	5 (73%)
TOTAL	87	52 (60%)	35 (40%)

4.5.3.2 Protocol deviations

During the trial there were no serious protocol breaches, but 17 protocol deviations (Table 26). Ten related to CRF completion and data entry, and seven were directly related to participants, which are outlined below.

One participant was approached and provided with information about the study during pregnancy. She delivered shortly thereafter and then contacted the study team to say she wished to be enrolled. As she had received information before birth (both verbal and written) and was keen to participate, she was consented postpartum (day 1). A second potential participant was approached by a research midwife (after discussion with her direct care team) as she was thought to be antenatal. In fact, she was still in hospital after delivery. This woman was very keen to be involved in the research study following the initial approach, and therefore was screened and consented postpartum.

One participant was randomised to self-management by a research midwife but was not added to the telemonitoring website. Therefore, she was unable to submit readings for the first three days after discharge from hospital until the error was identified and rectified by the CI.

One participant had her baseline visit conducted on day 11 (should be day one to six after birth) and after hospital discharge, as the research midwife at the site was away and there was no notification to the central trial team that she had given birth. She was keen to continue with the study, and was

therefore randomised. She was randomised to usual care so there was no impact on delivery of the intervention. This was subsequently avoided as it had the potential to introduce bias. The decision was taken (whilst blind to her results) to include this patient's data in the primary analysis.

Three participants were randomised in error (Figure 19), none were aware of their allocation: two participants were randomised prior to their baseline visit being finalised, and these participants then declined to continue to participate in the study. One participant was randomised during the baseline visit; before it became apparent she was no longer eligible (all antihypertensive medications discontinued).

Table 26: SNAP-HT protocol deviations^{§§}

June 2015	One participant screened and consented postpartum (having been approached during pregnancy) One participant approached, screened and consented postpartum (as research midwife unaware she had given birth) One participant randomised in error (did not wish to continue) <i>Two CRFs labelled with the incorrect participant study ID on the first page</i>
July 2015	One participant randomised in error (had become ineligible) <i>One screening CRF completed in duplicate as original initially retained by participant and then returned</i>
August 2015	<i>One discontinuation CRF labelled with the incorrect participant study ID</i>
September 2015	<i>One CRF labelled with incorrect study ID, identified before data entry and corrected</i>
November 2015	<i>One CRF not signed</i>
December 2015	One participant randomised to self-management but not added to the telemonitoring website, and therefore she was unable to submit readings for the first three days after discharge from hospital <i>One CRF had the incorrect participant study ID on one page</i>
January 2016	<i>One CRF not signed</i> <i>One CRF had the incorrect participant study ID on one page</i>
February 2016	<i>One CRF had the incorrect participant study ID on one page</i>
March 2016	Baseline visit conducted outside scheduled time window, and after hospital discharge
April 2016	One participant randomised in error (did not wish to continue)

4.5.3.3 Feasibility outcomes

The recruitment rate for the study was 91/188 (48%) of all approached potential participants, and 91/153 (59%) of those approached who were eligible. The overall randomisation rate per month was

Abbreviations: CRF = case report form

^{§§} Protocol deviations relating to CRFs and data entry in italics

1.5 participants per site per month. The retention rate to six-weeks was 84/91 (92%), and to the end of the study (six-months) 82/91 (90%). Amongst the 82 complete cases, 403/410 (98%) follow-up visits were completed, 380/410 (93%) within the pre-defined time windows (Table 27).

Table 27: Feasibility measures

Recruitment ***			
Recruitment rate:	48% (91 randomised, 188 approached potential participants) 59% (91 randomised, 153 eligible approached potential participants)		
Recruitment rate per month:	1.5 participants randomised per site per month (91 randomised, cumulative 59.2 months recruiting period)		
Consent rate:	54% (101 consented, 188 approached potential participants)		
Conversion rate: consented to randomised	90% (91 randomised, 101 consented)		
Retention rate	Whole population (n = 91)	Intervention (n = 45)	Control (n = 46)
6-months (end of study)	90% (82)	89% (40)	91% (42)
6-weeks	92% (84)	91% (41)	93% (43)
Compliance rate	Whole randomised population (n = 91)	Complete cases (n = 82)	
Study follow-up visits (3 – 7) attended within pre-defined time window	85% (388/455)	93% (380/410)	
Study follow-up visits (3 – 7) attended	91% (412/455)	98% (403/410)	

4.5.3.4 Blood pressure outcomes

86/91 women contributed data for analysis of the secondary outcomes (Figure 19). 75/86 provided complete follow-up data (i.e. no missed follow-up visits), 7/86 finished follow-up but missed one of the interim visits and a further 4/86 withdrew before the end of the study but contributed some data.

Overall, women in the intervention group had a lower mean BP postpartum compared to women in the control group (Figure 23, Table 28). The adjusted difference in the mean BP readings was greatest at six weeks postpartum. For all measures at this time point, the 95% confidence intervals for the adjusted mean differences did not cross zero: -5.2mmHg (95% confidence interval -9.3 to -

*** Patients were consented pre-delivery and randomised if they remained eligible and willing post-delivery

1.2) / -5.8mmHg (95% confidence interval -9.1 to -2.5) for the mean of the second and third readings. Mean DBP was lower in the intervention group from four weeks to six months postpartum (Table 28). In a sensitivity analysis, the adjusted mean differences between the groups for the mean of the second to sixth readings were similar at all time points (Table 28).

The adjusted between-group difference for the mean DBP (mean of second and third readings) across all follow-up visits was -3.7mmHg (95% confidence interval -6.3 to -1.1). No significant between-group difference was seen in the mean SBP across visits, however the MAP was consistently lower in the intervention group, and if the mean of the second to sixth readings was used, the 95% confidence interval did not cross zero (Table 29). Participants in the intervention group were more likely to have BP readings inside the target range (systolic and diastolic) at six weeks postpartum than were those in the control group (Table 30): adjusted odds ratio 8.0 (95% confidence interval 2.1 to 30.6) for the mean of second and third readings. Only a very small number of readings from both groups were outside the safety ranges (intervention group 2/203 readings, 1.0%; control group 4/209 readings, 1.9%) (Table 31).

To explore potential mechanisms for the differences observed in BP between groups, the profile (Table 28) and duration (Table 32) of postnatal antihypertensive treatment were calculated. At baseline, all women in both groups were taking antihypertensive medication (Table 22), as per the inclusion criteria, and the median WHO defined daily doses were similar at each follow-up visit in the two groups (Table 28). By six months, only one woman (2.5%) from the intervention group and two women (4.8%) from the control group remained on antihypertensive treatment (Table 28). Mean treatment duration (Table 32) was 39 days (SD 35) in the intervention group and 49 days (SD 42) in the control group: adjusted difference -12 days (95% confidence interval -30 to 6). Postpartum treatment duration was positively skewed, so the medians and interquartile ranges are also reported (Table 32) (intervention group 29 days (17-49), control group 40.5 days (22.5-58)).

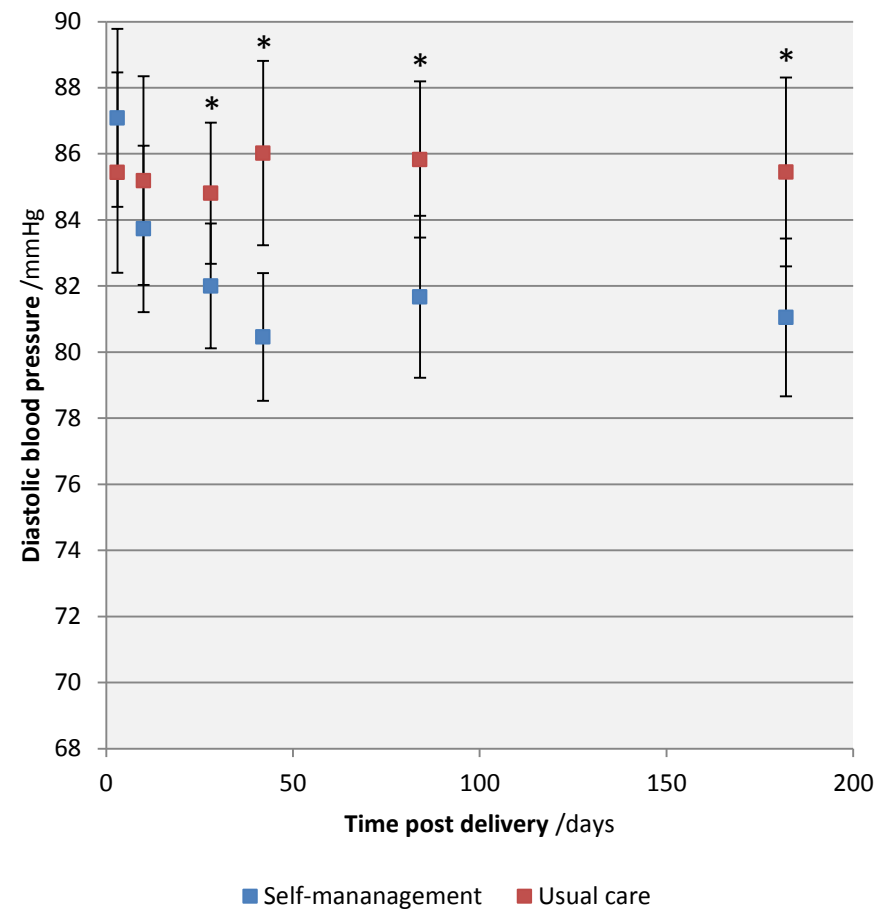
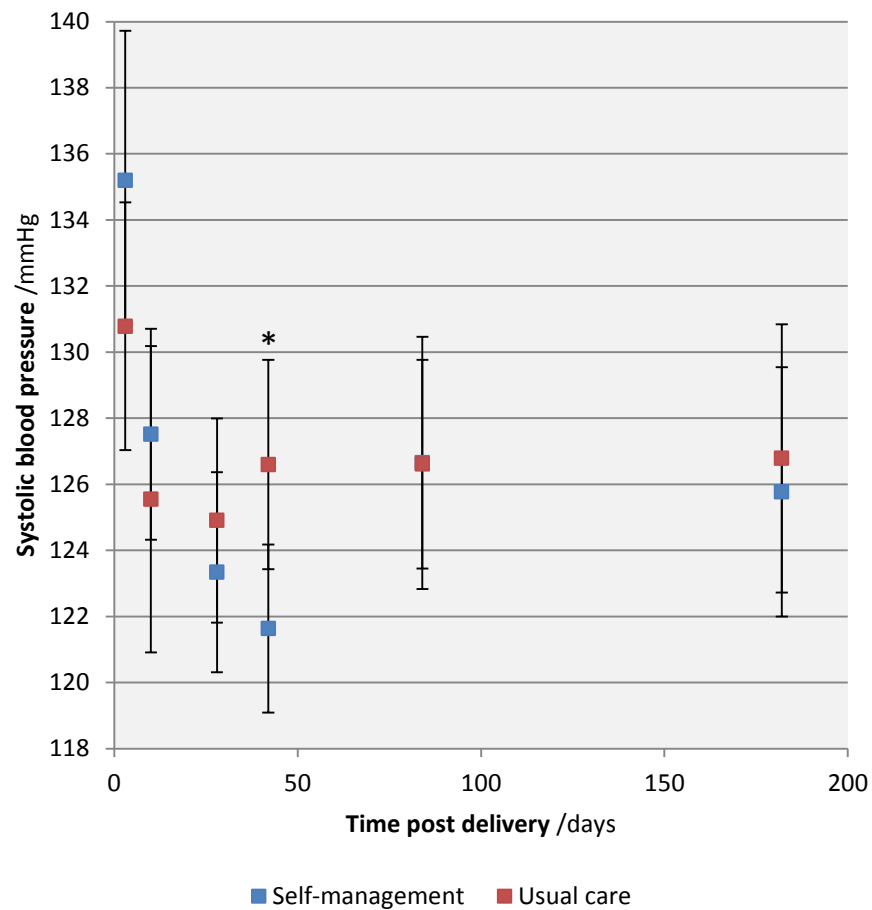


Figure 23: Raw mean systolic and diastolic blood pressures across follow-up

* Denotes where 95% confidence interval around adjusted difference does not cross zero

Table 28: Mean follow-up blood pressure readings

		Baseline Day 3 (PN day 1-6)	Visit 1 Day 10 (PN day 8-14)	Visit 2 4 weeks (PN day 21-35)	Visit 3 6 weeks (PN day 36-49)	Visit 4 12 weeks (PN day 77-91)	Visit 5 26 weeks (PN day 168-196)
Number of observations (I / C)		45 / 46 [*]	41 / 42	41 / 42	41 / 42	40 / 41	40 / 42 [†]
AHT treatment (I / C) frequency (%)		45 (100%) / 45 (100%)	38 (93%) / 38 (91%)	22 (54%) / 30 (71%)	14 (34%) / 19 (45%)	5 (13%) / 8 (20%)	1 (3%) / 2 (5%)
WHO defined daily dose AHT treatment (I / C) median (IQR)		1 (0.7 to 1.5) / 1 (0.7 to 1.7)	1 (0.4 to 1.4) / 1 (0.7 to 1.5)	0.3 (0 to 0.7) / 0.4 (0 to 1)	0 (0 to 0.3) / 0 (0 to 0.7)	0 (0 to 0) / 0 (0 to 0)	0 (0 to 0) / 0 (0 to 0)
SBP	I	<i>Readings 2 & 3 mean (SD) /mmHg[‡]</i>	135.2 (15.5)	127.5 (10.9)	123.3 (10.4)	121.6 (8.7)	126.7 (13.1)
		<i>Readings 2 to 6 mean (SD) /mmHg[§]</i>	135.0 (13.0)	127.0 (10.5)	122.4 (8.8)	121.7 (8.3)	125.9 (11.6)
	C	<i>Readings 2 & 3 mean (SD) /mmHg</i>	130.8 (13.0)	125.5 (16.0)	124.9 (10.7)	126.6 (11.0)	126.6 (10.9)
		<i>Readings 2 to 6 mean (SD) /mmHg</i>	131.2 (12.2)	126.2 (14.8)	124.4 (10.2)	125.6 (10.2)	126.6 (11.8)
	Adj. Δ (I – C)^{**,††}	<i>Δ mean of readings 2 & 3 (95% CI) /mmHg</i>	4.5 (-1.2 to 10.3)	1.6 (-3.9 to 7.1)	-1.8 (-6.1 to 2.6)	-5.2 (-9.3 to -1.2)*	-0.1 (-5.1 to 4.9)
		<i>Δ mean of readings 2 to 6 (95% CI) /mmHg</i>	3.9 (-1.2 to 8.9)	0.7 (-4.6 to 6.0)	-2.2 (-6.2 to 1.8)	-4.1 (-7.8 to -0.3)*	-1.9 (-6.8 to 2.9)
DBP	I	<i>Readings 2 & 3 mean (SD) /mmHg</i>	87.1 (9.2)	83.7 (8.6)	82.0 (6.5)	80.5 (6.6)	81.0 (8.2)
		<i>Readings 2 to 6 mean (SD) /mmHg</i>	86.9 (8.9)	83.4 (7.6)	81.2 (6.5)	80.2 (6.5)	81.7 (7.7)
	C	<i>Readings 2 & 3 mean (SD) /mmHg</i>	85.4 (10.5)	85.2 (10.9)	84.8 (7.4)	86.0 (9.7)	85.5 (9.9)
		<i>Readings 2 to 6 mean (SD) /mmHg</i>	86.2 (9.7)	85.8 (10.4)	84.0 (7.3)	85.8 (8.3)	85.1 (8.1)
	Adj. Δ (I – C)	<i>Δ mean of readings 2 & 3 (95% CI) /mmHg</i>	1.7 (-2.4 to 5.9)	-1.7 (-5.7 to 2.3)	-3.0 (-5.8 to -0.1)*	-5.8 (-9.1 to -2.5)*	-4.3 (-7.7 to -0.8)*
		<i>Δ mean of readings 2 to 6 (95% CI) /mmHg</i>	0.8 (-3.1 to 4.7)	-2.2 (-6.0 to 1.6)	-3.1 (-6.0 to -0.2)*	-5.7 (-8.7 to -2.6)*	-3.7 (-7.0 to -0.4)*
MAP	I	<i>Readings 2 & 3 mean (SD) /mmHg</i>	102.9 (10.6)	98.0 (8.6)	95.6 (7.1)	93.4 (6.5)	96.4 (9.4)
		<i>Readings 2 to 6 mean (SD) /mmHg</i>	102.6 (9.9)	97.9 (7.9)	94.9 (6.7)	94.0 (6.4)	96.4 (8.6)
	C	<i>Readings 2 & 3 mean (SD) /mmHg</i>	100.3 (10.7)	98.4 (12.2)	97.9 (8.0)	99.3 (9.6)	99.2 (8.5)
		<i>Readings 2 to 6 mean (SD) /mmHg</i>	101.2 (10.1)	99.3 (11.5)	97.5 (7.8)	99.1 (8.6)	98.9 (8.4)
	Adj. Δ (I – C)	<i>Δ mean of readings 2 & 3 (95% CI) /mmHg</i>	2.7 (-1.7 to 7.1)	-0.5 (-4.8 to 3.7)	-2.6 (-5.7 to 0.6)	-5.6 (-8.9 to -2.3)*	-2.8 (-6.6 to 0.9)
		<i>Δ mean of readings 2 to 6 (95% CI) /mmHg</i>	1.5 (-2.6 to 5.6)	-1.4 (-5.4 to 2.6)	-2.7 (-5.7 to 0.4)	-5.1 (-8.1 to -2.1)*	-3.9 (-7.5 to -0.3)*

Abbreviations: AHT = antihypertensive; C = control; 95% CI = 95% confidence interval; DBP = diastolic blood pressure; I = intervention; MAP = mean arterial pressure; PN = postnatal; SBP = systolic blood pressure; SD = standard deviation

*Denotes where the 95% confidence interval for the adjusted difference does not cross zero

^{*} In control group n = 44 for mean of readings 2-6 at baseline

[†] In control group n = 41 for mean of readings 2-6 at visit 5

[‡] 6 readings taken at each visit at 1-minute intervals: first reading discarded, mean of two readings (second and third) taken

[§] 6 readings taken at each visit at 1-minute intervals: first reading discarded, mean of five readings (second to sixth) taken

^{**} For differences between BP readings at baseline, a linear regression model was fitted with treatment group as the independent variable, adjusting for recruitment centre

^{††} For differences between BP readings at visits 1-5 a repeated measures mixed effects regression model was used, including the outcome with randomised group, time and an interaction between time and randomised group as fixed effects adjusting for recruitment site and BP at baseline, fitted as fixed effects with an unstructured covariance pattern

Table 29: Mean of mean blood pressure readings across follow-up

		Mean across visits 3-5 Day 10 – 6 weeks	Mean across visits 3-6 Day 10 – 3 months	Mean across visits 3-7 Day 10 – 6 months
SBP	I	Mean of readings 2+3 /mmHg (SD) ^{††}	124.4 (8.3)	125.0 (8.4)
		Mean of readings 2-6 /mmHg (SD) ^{§§}	123.8 (7.5)	124.4 (7.8)
	C	Mean of readings 2+3 /mmHg (SD)	125.6 (10.0)	125.8 (9.1)
		Mean of readings 2-6 /mmHg (SD)	125.3 (9.2)	125.5 (8.8)
	Adj. Δ (I – C) ^{***}	Δ mean of readings 2+3 /mmHg (95% CI)	-1.4 (-5.1 to 2.4)	-0.8 (-4.4 to 2.7)
		Δ mean of readings 2-6 /mmHg (95% CI)	-1.2 (-4.6 to 2.3)	-0.8 (-4.2 to 2.6)
DBP	I	Mean of readings 2+3 /mmHg (SD)	82.1 (5.0)	81.9 (5.0)
		Mean of readings 2-6 /mmHg (SD)	81.5 (5.0)	81.5 (4.9)
	C	Mean of readings 2+3 /mmHg (SD)	85.3 (8.0)	85.3 (7.4)
		Mean of readings 2-6 /mmHg (SD)	85.2 (7.5)	85.1 (7.1)
	Adj. Δ (I – C)	Δ mean of readings 2+3 /mmHg (95% CI)	-3.3 (-6.0 to -0.6)*	-3.5 (-6.1 to -0.9)*
		Δ mean of readings 2-6 /mmHg (95% CI)	-3.6 (-6.3 to -0.9)*	-3.7 (-6.2 to -1.1)*
MAP	I	Mean of readings 2+3 /mmHg (SD)	95.9 (5.6)	96.0 (5.6)
		Mean of readings 2-6 /mmHg (SD)	95.6 (5.2)	95.8 (5.3)
	C	Mean of readings 2+3 /mmHg (SD)	98.4 (8.3)	98.6 (7.7)
		Mean of readings 2-6 /mmHg (SD)	98.6 (7.8)	98.6 (7.4)
	Adj. Δ (I – C)	Δ mean of readings 2+3 /mmHg (95% CI)	-2.6 (-5.5 to 0.3)	-2.6 (-5.3 to 0.2)
		Δ mean of readings 2-6 /mmHg (95% CI)	-2.8 (-5.5 to -0.1)*	-2.7 (-5.3 to -0.1)*

Abbreviations: C = control; 95% CI = 95% confidence interval; DBP = diastolic blood pressure; I = intervention; MAP = mean arterial pressure; SBP = systolic blood pressure; SD = standard deviation

^{††} 6 readings taken at each visit at 1-minute intervals: first reading discarded, mean of two readings (second and third) taken

^{§§} 6 readings taken at each visit at 1-minute intervals: first reading discarded, mean of five readings (second to sixth) taken

^{***} A linear regression model for the mean combined BP at visits was fitted with treatment group as the independent variable, adjusting for recruitment centre and mean BP at baseline

Table 30: Proportion of blood pressure readings inside target range at follow-up

		Visit 1 Day 10 (PN day 8-14)	Visit 2 4 weeks (PN day 21-35)	Visit 3 6 weeks (PN day 36-49)	Visit 4 12 weeks (PN day 77-91)	Visit 5 26 weeks (PN day 168-196)
Number of observations (I / C)		41 / 42	41 / 42	41 / 42	40 / 41	40 / 42 ⁺⁺⁺
SBP <140mmHg >=100mmHg (on treatment) OR <140 mmHg (off treatment)	I	Mean of readings 2 & 3 frequency (%)	37 (90.2%)	39 (95.1%)	41 (100.0%)	35 (87.5%)
		Mean of readings 2 to 6 frequency (%)	38 (92.7%)	41 (100.0%)	40 (97.6%)	36 (90.0%)
	C	Mean of readings 2 & 3 frequency (%)	33 (78.6%)	38 (90.5%)	37 (88.1%)	36 (87.8%)
		Mean of readings 2 to 6 frequency (%)	33 (78.6%)	39 (92.7%)	40 (95.2%)	37 (88.1%)
	I:C	Adj. OR mean of readings 2 & 3 (95% CI) ⁺⁺⁺	2.7 (0.7 to 10.1)	2.3 (0.4 to 13.4)	. ^{§§§}	0.9 (0.2 to 3.7)
		Adj. OR mean of readings 2 to 6 (95% CI)	3.8 (0.9 to 16.3)	. ^{****}	1.6 (0.1 to 20.3)	2.1 (0.3 to 13.2)
DBP <90mmHg >=60mmHg (on treatment) OR <90 mmHg (off treatment)	I	Mean of readings 2 & 3 frequency (%)	28 (68.3%)	37 (90.2%)	38 (92.7%)	31 (77.5%)
		Mean of readings 2 to 6 frequency (%)	33 (80.5%)	36 (87.8%)	37 (90.2%)	32 (80.0%)
	C	Mean of readings 2 & 3 frequency (%)	29 (69.1%)	30 (71.4%)	26 (61.9%)	30 (73.2%)
		Mean of readings 2 to 6 frequency (%)	29 (69.1%)	32 (76.2%)	25 (59.5%)	31 (75.6%)
	I:C	Adj. OR mean of readings 2 & 3 (95% CI)	0.9 (0.3 to 2.5)	3.7 (1.0 to 13.1)*	8.0 (2.1 to 30.6)*	1.3 (0.5 to 3.9)
		Adj. OR mean of readings 2 to 6 (95% CI)	2.2 (0.7 to 7.4)	2.2 (0.7 to 7.3)	6.9 (2.0 to 24.0)*	1.3 (0.5 to 3.9)
BP SBP <140mmHg >=100mmHg AND DBP <90mmHg >=60mmHg (on treatment) OR SBP <140mmHg AND DBP <90mmHg (off treatment)	I	Mean of readings 2 & 3 frequency (%)	27 (65.9%)	37 (90.2%)	38 (92.7%)	30 (75.0%)
		Mean of readings 2 to 6 frequency (%)	33 (80.5%)	36 (87.8%)	36 (87.8%)	32 (80.0%)
	C	Mean of readings 2 & 3 frequency (%)	26 (61.9%)	30 (71.4%)	26 (61.9%)	30 (73.2%)
		Mean of readings 2 to 6 frequency (%)	26 (61.9%)	31 (73.8%)	25 (59.5%)	31 (75.6%)
	I:C	Adj. OR mean of readings 2 & 3 (95% CI)	1.2 (0.4 to 3.2)	3.7 (1.0 to 13.1)*	8.0 (2.1 to 30.6)*	1.2 (0.4 to 3.3)
		Adj. OR mean of readings 2 to 6 (95% CI)	3.3 (1.0 to 10.6)*	2.5 (0.8 to 8.3)	5.4 (1.7 to 17.6)*	1.3 (0.5 to 3.9)

Abbreviations: BP = blood pressure; C = control; 95% CI = 95% confidence interval; DBP = diastolic blood pressure; I = intervention; PN = postnatal; SBP = systolic blood pressure; SD = standard deviation

* Denotes where the 95% confidence interval for the adjusted odds ratio does not cross one (where lower limit of confidence interval is given as 1.0 rounded to one decimal place, this was marked as not crossing one only where the true value was >1.0)

⁺⁺⁺ n = 41 for mean of readings 2-6

⁺⁺⁺ Adjusted odds ratios calculated using logistic regression model, adjusting for recruitment site

^{§§§} Unable to apply logistic regression model as 100% of intervention group in target range

^{****} Unable to apply logistic regression model as 100% of intervention group in target range

Table 31: Proportion of blood pressure readings outside safety ranges at follow-up

	Intervention Frequency (%)	Control Frequency (%)
<i>Number of participants (total randomised)</i>	45	46
<i>Participants included in secondary analysis</i>	41	45
<i>Total number of time points where BP measured</i>	203	209
SBP readings ≥ 160mmHg		
Mean of readings 2+3 /mmHg [*]	2 (1%)	4 (2%)
Mean of readings 2-6 /mmHg [†]	2 (1%)	3 (1%)
DBP readings ≥ 110mmHg		
Mean of readings 2+3 /mmHg	0 (0%)	0 (0%)
Mean of readings 2-6 /mmHg	0 (0%)	1 (1%)
SBP readings < 90mmHg (on treatment)		
Mean of readings 2+3 /mmHg	0 (0%)	2 (1%)
Mean of readings 2-6 /mmHg	0 (0%)	0 (0%)

Table 32: Duration of postnatal antihypertensive treatment

Postnatal antihypertensive treatment	Intervention	Control	Adjusted Δ means (I-C) (95% CI)
<i>Number of participants who completed follow-up, stopped antihypertensive treatment and for whom data available</i>	39[‡]	36[§]	
Mean duration (SD) /days	39.3 (35.2)	49.4 (41.8)	-12.1 (-30.2 to 5.9) ^{**}
Median duration (IQR) /days	29 (17 to 49)	40.5 (22.5 to 58)	

4.5.3.5 Safety outcomes

During the trial 11 SAEs were reported (Table 33). Three were unrelated to BP, but eight women were readmitted to hospital with high or low BP, all within the first two weeks postpartum, five from the self-management group. All were still taking their antihypertensive medications from discharge, and none had yet begun to down-titrate. Reported side effects were similar between both groups

Abbreviations: BP = blood pressure; C = control; CI = confidence interval; DBP = diastolic blood pressure; I = intervention; IQR = interquartile range; PNRA = postnatal readmission; SAE = serious adverse events; SBP = systolic blood pressure; SD = standard deviation

^{*} 6 readings taken at each visit at 1-minute intervals: first reading discarded, mean of two readings (second and third) taken

[†] 6 readings taken at each visit at 1-minute intervals: first reading discarded, mean of five readings (second to sixth) taken

[‡] 40 participants completed follow-up; 1 participant remained on antihypertensive treatment at the end of the study

[§] 42 participants completed follow-up; 2 participants remained on antihypertensive treatment at the end of the study; 4 participants had incomplete medication end date data and were therefore excluded from this analysis

^{**} Adjusted difference calculated using linear regression model, with treatment group as the independent variable and adjusting for recruitment centre and mean arterial pressure at baseline

with the most commonly reported being dizziness (13.9% in the intervention group, 11.0% in the control group) (Table 33). Other side effects reported included headaches, fatigue, dry mouth and weakness.

Table 33: Postnatal readmissions and safety data

	Intervention Frequency (%)	Control Frequency (%)	Adjusted relative risk (95% CI) ^{††} or Incidence rate ratio (95% CI) ^{††}
<i>Total randomised participants</i>	45	46	
<i>Participants included in secondary analysis</i>	41	45	
Serious adverse events (SAE)^{§§}			
Number of participants with ≥1 SAE	7 (15.6%)	4 (8.7%)	2.0 (0.6 – 6.2) ^{***}
Total SAE episodes	7 (15.6%)	4 (8.7%)	1.8 (0.5 – 6.2) ^{†††}
Number of participants with ≥1 BP-related SAE	5 (11.1%)	3 (6.5%)	1.7 (0.4 – 6.8) ³
Total BP-related SAE episodes	5 (11.1%)	3 (6.5%)	1.7 (0.4 – 7.2) ⁴
Most common side effects related to antihypertensive medication (reported across follow-up)^{†††,§§§}			
Dizziness	15 (13.9%)	13 (11.0%)	
Headache	8 (7.4%)	9 (7.9%)	
Fatigue	5 (4.7%)	7 (5.9%)	
Dry mouth	4 (3.7%)	6 (5.1%)	
Weakness	4 (3.8%)	4 (3.4%)	
Stiff joints	6 (5.6%)	0 (0%)	
Flushed	0 (0%)	3 (2.5%)	
Shortness of breath	2 (1.9%)	0 (0%)	

4.5.3.6 Quality of life outcomes

No significant difference was seen between groups at any time point (screening, six weeks or six months) in participants' mean self –reported overall quality of life score, or in any of five separate quality of life domains, using the EQ-5D-5L self-administered questionnaire (Table 34).

Abbreviations: BP = blood pressure; 95% CI = 95% confidence interval; PNRA = postnatal readmission; SAE = serious adverse event

^{††} For binary outcomes (participants with ≥1 readmission or SAE)

^{††} For count outcomes (number of separate readmissions or SAEs)

^{§§} All SAEs were postnatal readmissions, and vice versa. There were no SAEs which did not involve postnatal readmissions.

^{***} Log binomial model fitted to the data with randomised group and recruitment site as covariates. Adjusted relative risks and 95% confidence intervals presented.

^{†††} Negative binomial model fitted to the data to compare randomised groups. The dependent variable was the number of readmissions while the explanatory variables included randomised group and recruitment site. Incident rate ratios and 95% confidence intervals presented.

^{†††} Side effects where >1 incidence reported from one or both study groups

^{§§§} For side effects percentages calculated using total frequency for each group divided by the number of occasions where side effects asked about (taking antihypertensive medication and data not missing)

Table 34: EQ-5D-5L scores

		Screening Antenatal, pre-randomisation		Visit 3 6 weeks		Visit 5 6 months	
		I	C	I	C	I	C
<i>Number of observations</i>		45	45	39	41	40	42
Mobility *	<i>Mean (SD)</i>	1.3 (0.6)	1.3 (0.7)	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)	1.0 (0.2)
	<i>Δ[†] I-C (95% CI)</i>	-0.0 (-0.3 to 0.2)		-0.1 (-0.2 to 0.1)		0.1 (-0.0 to 0.2)	
Self-care [‡]	<i>Mean (SD)</i>	1.1 (0.3)	1.1 (0.3)	1.0 (0.2)	1 (0)	1.1 (0.4)	1 (0)
	<i>Δ I-C (95% CI)</i>	0.1 (-0.1 to 0.2)		0.0 (-0.0 to 0.1)		0.1 (-0.0 to 0.2)	
Usual activities [§]	<i>Mean (SD)</i>	1.5 (0.6)	1.6 (1.0)	1.1 (0.4)	1.0 (0.2)	1.2 (0.5)	1.0 (0.2)
	<i>Δ I-C (95% CI)</i>	-0.1 (-0.5 to 0.2)		0.1 (-0.0 to 0.2)		0.2 (0.0 to 0.3)	
Pain / discomfort **	<i>Mean (SD)</i>	1.6 (0.6)	1.8 (0.9)	1.2 (0.5)	1.2 (0.6)	1.3 (0.7)	1.2 (0.4)
	<i>Δ I-C (95% CI)</i>	-0.2 (-0.5 to 0.1)		0.0 (-0.2 to 0.3)		0.1 (-0.2 to 0.4)	
Anxiety / depression ^{††}	<i>Mean (SD)</i>	1.4 (0.6)	1.4 (0.6)	1.1 (0.5)	1.1 (0.5)	1.1 (0.3)	1.2 (0.6)
	<i>Δ I-C (95% CI)</i>	-0.2 (-0.5 to 0.1)		-0.0 (-0.2 to 0.2)		-0.1 (-0.3 to 0.1)	
EQ-5D-5L VAS ^{††}	<i>Mean (SD)</i>	76.3 (16.9)	68.8 (20.4)	85.3 (11.0)	85.9 (13.5)	86.2 (10.7)	89.2 (8.9)
	<i>Δ I-C (95% CI)</i>	7.5 (-0.4 to 15.3)		-1.0 (-6.3 to 4.3)		-3.3 (-7.5 to 0.9)	

Abbreviations: C = control; 95% CI = 95% confidence interval; I = intervention; SD = standard deviation; VAS = visual analogue scale

* **Scale:** 1 = no problems in walking about; 2 = slight problems in walking about; 3 = moderate problems in walking about; 4 = severe problems in walking about; 5 = unable to walk about

[†] Adjusted difference between groups calculated at follow-up visits using a mixed effects repeated measures regression model, adjusting for EQ5D5L VAS score at screening and recruitment site; difference in raw means presented for screening visit

[‡] **Scale:** 1 = no problems washing or dressing myself; 2 = slight problems washing or dressing myself; 3 = moderate problems washing or dressing myself; 4 = severe problems washing or dressing myself; 5 = unable to wash or dress myself

[§] **Scale:** 1 = no problems doing my usual activities; 2 = slight problems doing my usual activities; 3 = moderate problems doing my usual activities; 4 = severe problems doing my usual activities; 5 = unable to do my usual activities

^{**} **Scale:** 1 = no pain or discomfort; 2 = slight pain or discomfort; 3 = moderate pain or discomfort; 4 = severe pain or discomfort; 5 = extreme pain or discomfort

^{††} **Scale:** 1 = not anxious or depressed; 2 = slightly anxious or depressed; 3 = moderately anxious or depressed; 4 = severely anxious or depressed; 5 = extremely anxious or depressed

^{††} **Scale:** 100 = the best health you can imagine; 0 = the worst health you can imagine

4.5.3.7 Exploratory outcomes

Evaluation of the submitted BP readings (intervention group) downloaded from the telemonitoring website (section 4.3.4.3), showed that 36/40 (90%) complete cases submitted BP readings on at least alternate days whilst they remained on antihypertensive treatment (in line with the NICE recommendation(1)). The median participant compliance with daily readings, whilst on treatment, was 84.5% (IQR 66.2 – 98.4), and in total 71.1% (1075/1513) of the expected daily readings whilst on treatment were submitted. 7/40 (18%) participants had ‘overdue’ readings (section 4.3.5.1) whilst on treatment, but only 4/40 (10%) participants had more than one.

Comparison of BP readings from the telemonitoring website, with the BP readings from the memory of the home BP monitors, revealed a median participant accuracy of 94% (IQR 84.1 – 100). In total across the complete cases, 87% (926/1061) submitted daily readings were accurate (where data was available for comparison – duplicate readings and lost downloaded data were excluded from this analysis). 6% (68/1061) readings were inaccurate (non-identical systolic measurement, diastolic measurement or both). However, only 14 of these (1% of total) were submitted at a different BP threshold (Table 17), and therefore had the potential to influence the behaviour of the algorithm. A further 6% (67/1061) of submitted readings appeared fictitious: no corresponding reading downloaded from the monitor. Almost half (29/67, 43%) were provided by one participant. Five ‘fictitious’ readings (7%), from four participants, triggered a medication reduction step.

Comparison of the follow-up (or ‘office’) blood pressure measurements, with participants’ HBPM demonstrated that the HBPM tended to be significantly lower (both systolic and diastolic) than the clinic readings (range of raw mean differences across follow-up visits -3.2 to -3.8mmHg) (Table 35).

Table 35: Analysis of differences between clinic and home blood pressure readings in intervention group*

	Visit 1 Day 10 (PN day 8-14)	Visit 2 4 weeks (PN day 21-35)	Visit 3 6 weeks (PN day 36-49)	Visit 4 12 weeks (PN day 77-91)	Visit 5 26 weeks (PN day 168-196)	Mean across visits
Number of participants[†]	36	38	37	37	26	40 [‡]
Mean time Δ clinic BP and closest home BP /days	0.2 (0.4)	0.9 (1.4)	2.0 (3.0)	3.8 (4.3)	8.8 (7.3)	2.7 (2.0)
Mean time Δ clinic BP and second closest home BP /days	1.0 (0.5)	2.7 (2.8)	4.1 (3.4)	7.6 (4.5)	15.8 (7.2)	5.0 (2.7)
SBP						
Raw mean Δ (mean of two closest home readings and mean clinic reading [§]) (95% CI) /mmHg**	-3.7 (-7.2 to -0.3)*	-1.9 (-4.8 to 1.0)	0.2 (-3.0 to 3.4)	-7.2 (-10.7 to -3.6)*	-5.2 (-7.4 to -3.0)*	-3.8 (-5.6 to -2.1)*
Raw mean Δ (closest home reading and mean clinic reading) (95% CI) /mmHg ^{††}	-2.7 (-6.3 to 0.8)	-2.6 (-5.6 to 0.5)	0.1 (-3.8 to 3.9)	-7.5 (-11.3 to -3.8)*	-5.2 (-8.2 to -2.2)*	-3.5 (-5.2 to -1.7)*
DBP						
Raw mean Δ (mean of two closest home readings and mean clinic reading) (95% CI) /mmHg	-3.1 (-6.1 to -0.2)*	-3.4 (-5.7 to -1.1)*	-3.3 (-5.2 to -1.3)*	-5.3 (-8.0 to -2.6)*	-3.2 (-5.2 to -1.1)*	-3.2 (-4.6 to -1.9)*
Raw mean Δ (closest home reading and mean clinic reading) (95% CI) /mmHg	-2.5 (-5.9 to 0.9)	-3.9 (-6.3 to -1.5)*	-2.7 (-4.9 to -0.5)*	-6.9 (-9.5 to -4.3)*	-2.8 (-5.5 to -0.1)*	-3.2 (-5.0 to -1.6)*

Abbreviations: BP = blood pressure; 95% CI = 95% confidence interval; DBP = diastolic blood pressure; PN = postnatal; SBP = systolic blood pressure

* For all comparisons between home and 'office' blood pressure readings, paired two-sample t-test used for analysis.

* Denotes where 95% confidence interval does not cross zero

[†] Missing data where no 'office' measurement, or no downloaded HBPM data available. Data was excluded from analysis if more than 7 days between timing of 'office' and home readings if daily readings, or more than 4 weeks between timing of 'office' and home readings if weekly readings (off treatment)).

[‡] 40/45 randomised participants from the intervention group contributed data to these analyses (i.e. attended at least one research follow-up visit, and readings downloaded successfully from the home blood pressure monitor).

[§] In all analyses mean of second and third 'office' readings used for comparison.

** Mean 'office' reading compared with the mean of the two closest (in time) home BP readings downloaded from monitor. Where a participant took two (as per instructions), or more, readings less than ten minutes apart, the second reading was selected for this analysis.

^{††} Mean 'office' reading compared with the closest (in time) home BP reading downloaded from monitor.

4.5.4 Discussion

4.5.4.1 Main findings

This trial, for the first time, has shown that self-management of BP after pregnancy is feasible: women were happy to be randomised, and the trial had a low attrition rate (<10%) and high fidelity rate (>90%) (Table 27). In terms of the pre-defined criteria for success of the pilot study, an attrition rate of <10% and a compliance rate of >90% were achieved. All sites contributed $\geq 5\%$ of the total study participants. The randomisation rate per site per month was 1.5 participants. In total the study was open for 56.4 weeks (although not all sites were open for this entire period), giving an approximate randomisation rate of 1.5 participants per week across all the sites. This fell short of the initial target of 3 participants per week. However, given the high recruitment rate among approached, eligible potential participants (59%) this may reflect difficulty in identifying and accessing potential participants, or a smaller pool of eligible patients than predicted (section 3.5), as opposed to women's reluctance to be involved in the study. With respect to the primary outcome of evaluating the feasibility of running the study on a larger scale in the future, this should be practicable with some modifications to the protocol.

Whilst this trial was not powered to detect a difference in BP control between groups, several different measures of postpartum BP control indicated this was improved by self-management. Women who self-managed had on average lower DBP from four weeks to the end of follow-up and lower SBP at six weeks (Table 28). At six weeks, the intervention group were significantly more likely to have BP readings inside the target ranges (Table 30), which provides reassurance that the lower mean BP readings, seen in the intervention group at this time point, do not result from some individuals being over-treated and artificially skewing the mean. Very few participants in either group had BP readings outside the safety thresholds (Table 31).

Almost all women in both groups (>95%) were off antihypertensive treatment by six months, and the intervention group showed a tendency towards a shorter overall duration of treatment (adjusted

mean difference -12 days (95% confidence interval -30 to 6)). Therefore, it would seem that the observed treatment effect is not mediated through increased antihypertensive use, but perhaps through more appropriately targeted prescribing, and potentially improved adherence, as has been demonstrated in essential hypertension (292). The evidence base for self-monitoring in essential hypertension has not previously suggested that lifestyle alterations (including diet and exercise modifications) are the mechanism (292).

4.5.4.2 Safety

There were a small number of SAEs in both groups, without serious BP-related morbidity, or mortality. Eight were related to BP control, split across the two groups (five in the intervention group, three in the control group). As none of the five women in the intervention group had yet started to down-titrate their antihypertensive medication, and all were readmitted to hospital within the first two weeks after birth, on the antihypertensive regime they had been discharged from hospital, these SAEs were considered unrelated to the intervention. Similar rates of side effects related to antihypertensive medication were reported in the two groups.

4.5.4.3 Intervention fidelity

The exploratory analyses suggest good adherence with daily readings whilst on treatment, similar to that reported for HBPM in essential hypertension: in the TASMINH2 study 72% of those allocated to telemonitoring self-managed their BP, and completed 90% of the expected measurements (144).

The accuracy level was good, but not as high as previously reported for HBPM in pregnancy: Waugh *et al.* (2003) reported an accuracy level of 97% amongst 72 participants (133). However, their study period was only 5-7 days, compared to this population who were submitting daily readings whilst at home on antihypertensive treatment for a mean 37.8 days.

4.5.4.4 Strengths and limitations

This trial benefited from being run across four NHS Trusts (five distinct hospital sites), with participants being recruited from a relatively wide geographic area (Figure 20 and Figure 21). No limitations were placed upon prescribing choices postpartum – participants were taking a range of different antihypertensive medications, reflecting usual clinical care. In contrast to the previously published intervention trials in postpartum hypertension (Chapter 2), the BP control data extends to 6-months postpartum. Randomisation with robust allocation concealment limited selection bias, and produced two study groups with similar baseline characteristics (Table 22).

The conclusions are limited because this was a feasibility study, not powered to detect a difference in the secondary outcomes. However, the size of the BP improvements observed and in the case of DBP, the continuation of the difference well after the initial intervention suggests that that self-management may have a significant place in the postpartum management of HDP. Extrapolating the results of a feasibility study into a larger trial or implementation requires some tempering in terms of the likely improvements in fidelity and follow-up from smaller scale studies. The trial's small size meant that the trial team only consisted of two core members who did the majority of recruitment and follow-up, with two additional research midwives based at two research sites. This may have improved the fidelity with which the intervention was delivered, and as such give a falsely elevated impression of the effectiveness, which may be expected in normal clinical practice, or within a larger RCT. However, this should be balanced against the likely impact from the Hawthorne effect: all participants in the trial may be influenced simply by participation in research and the experience of being observed, but this may especially impact upon the effectiveness of the usual care encountered in the study (293).

The trial population was largely white (>80%) and middle-class (59% had IMD scores in the first or second quintile), which limits the generalisability of the findings. The trial was open-label, as the

nature of self-monitoring precluded blinding participants. However, the BP outcome data were collected using the automated mode of a validated, oscillometric monitor to limit detection bias.

4.5.4.5 Comparison to the published literature

No previous randomised trials have reported on the feasibility or effectiveness of self-management of antihypertensive treatment in the postnatal period. A recently published non-randomised study (n=32) has evaluated compliance with HBPM and telemonitoring using an SMS service in the first seven days after discharge, in women with HDP (138, 250). However, this study did not include a control group, nor did it assess automating down-titration.

The systematic review (Chapter 2) revealed that no previous trials have evaluated self-management of hypertension and only three identified studies reported follow-up periods of six months or longer. Two evaluated the use of indapamide versus methyldopa in postnatal hypertension, in open-label RCTs, in small study populations (both n=30) and showed no difference between groups in BP control at six to 12 months (196, 212). The third was an open-label RCT comparing labetalol with nifedipine in postnatal hypertension (n=50). No difference was seen in BP control between the two groups, and the long-term follow-up data was limited by significant missing data (only 20% collected at six weeks), and it is unclear how many women provided follow-up data about total treatment duration at six months (199). Therefore, from the literature review, this is the first time any intervention has been reported to produce a persistent reduction in DBP on an ongoing basis in the medium-term following birth.

The magnitude of the BP difference achieved by self-titration in essential hypertension seems to be reproducible in this population, albeit achieved after six weeks from down titration rather than 12 months from up titration (118, 119). Intriguingly, in this context the difference in DBP persisted off treatment for the vast majority of women.

4.5.4.6 *Meaning of the study*

The persisting differences in diastolic BP, even off treatment, may reflect an effect of tighter BP control in the first six weeks: during hypertensive pregnancies, adverse cardiac and vascular remodelling occurs, which then partially resolves postpartum (294). The tighter BP control may have had a beneficial impact on this postpartum recovery, thereby re-establishing a haemodynamic situation that maintains a lower long-term BP. Observational data have previously shown that a higher BP at six-weeks postpartum correlates with a greater risk of hypertension up to ten years later (111). It may be through this mechanism that hypertensive disorders of pregnancy become an independent risk factor for cardiovascular disease later in life (108, 112). Better BP control during the puerperium could modulate this long-term risk and it will be important to confirm this in subsequent self-management studies.

The improvement in diastolic BP, without corresponding reduction of systolic BP at six months, may reflect predominant improvements in peripheral vascular resistance with fairly static (or less dramatic) changes in cardiac output and arterial compliance, i.e. some reversal of the isolated diastolic hypertension seen classically developing in 30 to 50 year olds. The observed difference in DBP is consistent with the previously published observation that whilst cardiac size and systolic function were preserved in women 6-13 years following a pre-eclamptic pregnancy, there was evidence of abnormal diastolic relaxation when compared to healthy controls (295). A further study demonstrated significantly higher resistance throughout the arterial system, measured by echocardiography and tonometry, at six months and three years postpartum in women with pre-eclampsia (n=40) than in controls with a normal pregnancy (n=65) (296).

4.5.5 *Conclusions*

Collectively these data imply that self-management may result in better BP control postpartum, and that this effect may persist beyond the end of antihypertensive treatment. However, this study was not powered for these outcomes, and was certainly too small to adequately evaluate substantive

maternal morbidity outcomes. The recruitment and retention rates suggest expanding the study would be feasible. A large-scale RCT with BP as the primary outcome is warranted to further explore the hypothesis that improved short-term BP control in the puerperium can positively modulate long-term BP and potentially cardiovascular risk. From these pilot data, self-management would seem to be an effective and acceptable intervention to implement in order to test this (Chapter 5). The literature review (Chapter 2) provides no evidence for any alternative postnatal hypertension management strategy that has demonstrated similar results.

Chapter 5: Participant experience of self-management of postnatal antihypertensive treatment: a qualitative sub-study

5.1 Objectives

In this chapter the results from the qualitative study embedded within the SNAP-HT trial will be presented. This was undertaken to better understand views of patients as to the acceptability of self-management in the routine management of HDP after birth following discharge from hospital. The aim was to assess the experience of participants in both study groups (usual care and self-management) using audio-recorded semi-structured interviews to identify and explore factors related to the successful (or otherwise) implementation of the self-management intervention.

This study assessed whether patients were happy to employ self-management techniques during the postpartum period, and whether participants perceived any advantages or disadvantages of this model when compared to usual care. The intention of conducting this research alongside the pilot study was to enhance understanding of the processes by which the self-management intervention was adopted and implemented, and to assist with design of a maximally user-friendly self-management solution for this cohort of patients moving forwards to a larger scale RCT, and with a view to rolling out the intervention into clinical practice (167). Important aspects of the interviews were: identifying perceived barriers; where similarities and differences in perception lie; appropriate behaviours and information sharing between patient, practitioner and practice staff necessary to maximise successful management; and patient satisfaction. This approach was chosen as it is now widely acknowledged that qualitative work conducted alongside clinical trials can complement quantitative data, by providing a different perspective about factors contributing to the success or failure of the tested intervention (section 1.10).

The theoretical orientation and methodological approach to this sub-study will be described first, before presenting the findings and drawing conclusions.

5.2 Background

Linked qualitative studies have been used successfully alongside other intervention studies examining self-management of essential hypertension, and the management of hypertension in pregnancy. During the TASMINH2 RCT evaluating self-management for essential hypertension, semi-structured interviews were conducted with a subset of participants receiving the intervention, and their family members (279). This concluded that participants felt confident about HBPM, and believed that multiple readings were more valid than a one-off visit to a healthcare professional. Participants felt more comfortable increasing their antihypertensive medication when their BP was substantially elevated, but less so with borderline readings. The authors likened this to the 'clinical inertia' seen amongst physicians when confronted with similar circumstances (279).

A mixed methods study (BP-Eth) sought to explore patterns of, and preferences for, different modalities of BP monitoring amongst different ethnic groups (297). Acceptability of different methods of monitoring was evaluated using a previously validated questionnaire, and focus groups were conducted to explore participants' experiences in greater depth. Self-monitoring was consistently the most acceptable mode of measurement, without variation by ethnicity. However, acceptability scores were significantly lower across all monitoring modalities for ethnic minorities compared with white British participants (298).

Following participation in the CHIPS (Control of Hypertension in Pregnancy Study) pilot study, women were invited to complete a postpartum questionnaire to evaluate their experience of their BP management, and participation in the study. 126/132 (96%) participants completed the questionnaire. At least 90% from both groups were satisfied with their care, and would be willing to participate again, and 60% of all women reported undertaking HBPM during the study, although this was not mandated by the trial protocol (139).

5.2.1 Theoretical approach

Qualitative research has a different agenda to quantitative research: quantitative studies may be interested in epidemiology or measures of effect size from an intervention, where qualitative studies may seek to explore explanations for certain behaviour patterns or reported phenomena (299).

Qualitative methodology needs to be informed by a theoretical perspective. Data analysis may be approached in either a deductive or an inductive fashion. Deduction is the approach typically taken in quantitative research: theoretical hypotheses are tested via data collection. Inductive processes are more commonly employed in qualitative research, where theory is generated from direct observation (300). This qualitative project had a fairly narrow defined purpose (section 5.1), so a relatively pragmatic approach was adopted: the sample was necessarily restricted by the trial entry criteria, and the interviewers inevitably brought their knowledge and beliefs about self-management to the interviews, and consequently whilst informed by grounded theory, a purist inductive approach was not adhered to. The interview schedules were informed by previous research and theories. However, despite these constraints, a grounded approach allowed the data to speak for itself and allowed theories to emerge

Glaser and Strauss (1967) first explicitly described grounded theory: theories generated through the process of data coding and analysis, in contrast to a priori, logico-deductive theories, tested experimentally through collection and analysis of data – as is the case with a null hypothesis in quantitative research. Grounded theories arise from the data. The authors propose that development of theories in this fashion is a means of arriving at theories, which are well suited to their uses, and limits the use of theories that do not fit well with the data upon which they are imposed. Any grounded theory's adequacy is therefore contingent on the process by which it is created. The authors emphasise that in the creation of grounded theory, theoretical sampling, data collection, coding and analysis should as far as possible be conducted simultaneously, and until data saturation is reached (section 5.2.3). This is the constant comparative method (301). Grounded

theory provides a set of systematic, rigorous and transparent steps by which to sample, collect, code and analyse qualitative data.

5.2.2 Qualitative interviews

Interviews form one of the central tenets of generated qualitative research methodology (302).

Qualitative interviews seek to explore the interviewee's own framework of meanings, and avoid imposition of the researcher's beliefs and structures where possible. Interviewees should be given sufficient time to explain their meanings, and interviewers should limit how directive they are in their questioning.

Three main types of qualitative interview are described commonly: structured, semi-structured and in-depth. Structured interviews consist of interviewers administering a questionnaire in a standardised fashion, which may have answers that are fixed choice, but generally provide free-text options. Semi-structured interviews utilise a looser structure, where open-ended questions are asked, and the interviewer has the opportunity to diverge from the 'script' to explore a participant's perspective in more detail. Questions may be asked in a different order depending on the progress and flow of the interview. In-depth interviews are even less structured: they may only explore one or two issues in substantially more detail. Further questions are generated by what the participant says, and are posed with the intention of clarification or adding more detail (299).

Patton (1987) provides some advice on both the topic and nature of good qualitative interview questions. He proposed they should be open-ended, empowering participants to expand their answer as opposed to encouraging a yes or no answer. Questions should be neutral, such that the interviewer avoids imposing their own beliefs upon the interviewee, and sensitive to potentially difficult topics. The language used should be clear, and understandable by the interviewee (303).

Field (1989) highlights some common pitfalls in qualitative interviewing, several of which are particularly pertinent to running a research study in a postnatal population, including interruptions,

competing distractions and the potential for the interviewers to start providing medical information or counselling, or present their own perspective (304).

In most settings, audio- or video-recording interviews are the preferred methods for reliably capturing qualitative data. The richness of information is preserved, and the process of note taking does not disturb the interview. Digital voice-recorders tend to be the current tool of choice. Good quality equipment, with which the interviewer is familiar, is crucial (305). Explicit consent is required for audio-recording during research.

5.2.3 Sampling in qualitative research

Sampling approaches in qualitative research are less prescriptive than those employed in quantitative research (306). Case selection can, however, have a profound impact on the ultimate quality of the data generated from qualitative interviews. As in quantitative research, inappropriate sampling has the potential to introduce bias, but the notion of 'appropriateness' in qualitative research is somewhat different: participants must be selected to meet the informational needs of the study; and selected informants must be willing to share their views with the interviewer, and be sufficiently articulate and reflective in order to do so (307).

Several different approaches to sampling in qualitative research have been described. Morse (1991) describes four approaches: purposeful, nominated, volunteer and total population sampling (307). Purposeful, or purposive, sampling selects participants according to the information needed by the study. The sampling process adapts during the study: initially participants with a broad, 'typical' knowledge of the subject are chosen, followed by those with particular, detailed knowledge. Lastly informants with 'atypical' experiences are sought such that the full breadth of phenomena is captured. Nominated sampling involves selecting a single participant, and using said participant to assist in selection and recruitment of the next participant. Volunteer samples rely on potential participants coming forward, and are dependent on adequate advertising of a study. Total population sampling is only feasible when the total number of potential informants is manageable.

Some informants may be strictly less 'useful', in terms of the information they are able to provide, but strengths of this approach are that no one feels excluded, and unexpected information may be captured. Such a sample can be subjected to 'secondary selection' where audio-recordings are only transcribed if the information is deemed useful, and saturation has not been reached.

Saturation is a concept utilised in a qualitative research to describe the point at which sufficient data have been collected and analysed to produce informational adequacy and a complete resulting theory: the origins of this notion lie in grounded theory (section 5.2.1). Theoretical saturation is defined as the point at which new data do not develop the emerging theory further (302): the categories are fully accounted for, and variability and relationships between them have been fully evaluated (308). As appropriate sampling in qualitative research intends to acquire rich information, in both depth and breadth, saturation is often utilised in quality assessment to assess sampling adequacy (309). However, it has been acknowledged that 'the saturation concept remains nebulous and lacks systematization' (Bowen, 2008), so simply mentioning that saturation was reached during sampling is insufficient. He suggests authors must provide evidence of saturation and the steps taken to ensure it was achieved (310).

However, Guest *et al.* (2006) assert that the literature surrounding both methodology and quality assessment in qualitative research is lacking detail about how to operationalise the concept of saturation. Their literature review found no evidence-based generalizable recommendations for non-probabilistic sample sizes required to reach saturation. Using data from sixty in-depth interviews, these authors documented the progressive extent of data saturation and variability over the course of a systematic data analysis, with the intention of establishing some measure of when saturation is likely to occur. They defined saturation as the point at which 'new information produces little or no change to the codebook' (section 5.2.4), and concluded this had largely occurred after analysis of 12 interviews, in terms of the overall codebook (88% of all codes had been

created), code definitions (58% of total revisions had occurred by this stage) and high frequency codes (i.e. those applied to multiple participants) (311).

In this sub-study, total population (within trial) sampling was practical due to the relatively small size of the overall pilot study. This approach was adopted to ensure no participants felt their views were excluded, and to limit any selection bias which may be introduced by applying an alternative sampling approach to a population well known to the research team.

5.2.4 Analysis

Thematic analysis involves coding, categorising and interpreting qualitative data. The first stage is data transcription. During transcription, and the data collection itself, the researcher begins to think about the data, and identify likely issues and concepts. Reading the first few transcripts the researcher starts to 'code' the data: codes are labels that are applied to segments of text. Codes that relate to each other can then be grouped into categories; some codes may belong in more than one category. This coding framework will be developed and adjusted over the course of the analysis. Once data has been coded and categorised, the researcher will map and summarise the data to develop conclusions and theory (312), which can then be placed into the context of pre-existing literature.

Ritchie and Spencer (1994), from the National Centre for Social Research, described a form of thematic analysis known as 'framework analysis'. This gives a slightly more systematic and prescriptive way to approach qualitative data, which they acknowledge can be unstructured, and at times unwieldy. They detail several uses of their proposed approach: to define concepts; map the range and nature of phenomena; create categorisations; find associations; seek explanations; and to develop new ideas and theory (313).

The stages they describe are similar to thematic analysis, but with more explicit labels. The first is familiarisation, where the researcher acquaints themselves with the data and lists key ideas and

recurrent themes, starting the processes of abstraction and contextualisation. This allows them to construct a thematic framework, identifying key issues, concepts and themes generated by familiarisation. Thematic frameworks will have headings and subheadings for the categorisation of data. The original framework is often descriptive, and will be refined through application to the first transcripts. Once a framework has been drafted the data can be indexed, with subheadings and headings applied. Gale *et al.* proposed using the terms codes (subheadings) and categories (headings), as for classical thematic analysis (314). At this stage, judgements are made about the significance and meanings of the data, and patterns and context will begin to emerge. Charting is the next step: the researcher extracts indexed data from their original context and inserts them under headings (categories) and subheadings (codes) in the thematic framework. Each key subject area (category or heading) will have its own chart within the framework. Subheadings (codes) occupy the columns, and cases the rows. Typically, the researcher creates a distilled summary of the data, with a reference to the original text. Finally, the researcher proceeds to mapping and interpretation, when they review the charts and research notes, comparing and contrasting the accounts, perceptions and experience of different participants. They will generate patterns and connections, and seek explanations and theory from the data (302, 313, 314).

Framework analysis requires that data must cover similar topics and key issues, and is most commonly used for analysis of semi-structured interview transcripts. Although it produces a more structured output of summarised data than some other approaches to qualitative data, the need for qualitative research skills for appropriate interpretation of the charts, and reflexivity and rigour are required in equal measure to other methods. Framework analysis is not derived from, or aligned with, a particular philosophy or theory, but whilst it is not driven by the generation of social theory, it can be a good technique for undertaking constant comparison (314).

5.3 Methods

Interviews were conducted with participants from both treatment groups who consented to participate in the qualitative sub-study (consent was taken alongside consent for the main study, prior to randomisation). The intention was to recruit a minimum of 50% of participants in each group (i.e. 50 women, 25 from each group), but total population sampling was adopted, so no limit was placed on the number of women who could be enrolled into this sub-study if they wished to participate.

A semi-structured interview approach was utilised, to provide a reproducible format for consistency across interviews, whilst also allowing for further explanation and divergence. Standard interview questions were developed from scratch to take into account the listed benefits of self-management in NHS policy and the constructs of normalisation process theory (section 1.10). There were five questions for both groups, and an additional five questions in the intervention group. Interview templates were developed (Appendix 16), where the participants were asked to provide a score (Likert scale 1 – 5) for each question. Established instruments such as the Patient Activation Measure (315), and the Partners in Health Scale Validated Questionnaire were used to validate the questions and the phrasing of the questions (316). Two researchers (the author and one research midwife) conducted all the follow-up interviews, both of whom had had training in and/or experience of conducting qualitative interviews.

At screening, baseline data relating to the first five interview questions were recorded, and any particular comments made by participants were documented. The semi-structured interviews were then conducted at the four week (visit 2) and six month (visit 5) visits. These were audio-recorded, with participants' explicit written consent, and lasted approximately 10-15 minutes on each occasion. At the interviews at four weeks, patients were asked for the structured response first followed by any comments. At the final follow-up visit at six months the aim was to gather more

detailed answers about participants' experiences so they were asked for to expand on their views followed by the structured response.

The interviews were transcribed verbatim into NVivo (computer-assisted qualitative data analysis software (317)) in order to capture all participant experiences, and reviewed for accuracy.

Transcribed interviews were coded thematically and analysed using the Framework method (section 5.2.4) (313). The coding framework (Table 36) was developed using a mixture of deductive and inductive approaches, in line with the pragmatic theoretical approach: That is, some of the categories were readily derived from the structured interview questions and literature review, whilst other categories and particularly the codes (subheadings) were created after reading through the interview transcriptions. The framework was developed whilst reading through the transcribed interviews, prior to formal coding, but was refined during the coding process. The framework was designed to allow coding of interviews from both groups, although some categories and codes (particularly those relating directly to telemonitoring and self-management) were more applicable to the intervention group.

The framework had eight categories. Substantial crossover does exist between some of these categories. The distinction was deliberately made between HBPM and telemonitoring and self-management. This allowed separation of perceived advantages of and concerns about HBPM, and the ability to integrate HBPM readings into a model of care including other healthcare professionals; from specific observations from women in the intervention group about the self-management approach adopted by this study, highlighting strengths of the system and areas for improvement. After coding, framework matrices were produced for each category and code, divided by treatment group, to allow detailed interpretation of the data and synthesis of connections and conclusions.

Table 36: Coding framework

Categories	Codes	
	Appointments	GP Midwife Practice nurse
Access to healthcare	Continuity of care	
	Handover of care	
	Travel	
	Strategies to improve access	
Time pressures	New baby	
	Other children	
	Special care baby unit admission	
	Time spent on self-management	
Communication with healthcare professionals	Confidence in communicating with healthcare professionals	
	Listening	
	Explanations	
	Knowledge base of healthcare professionals	
Information provision	Information from healthcare professionals	
	Written information	
	Online information	
	Past experiences	
Control	Other sources of information	
	Control of blood pressure	
	Understanding of blood pressure	
	Responsibility sharing	
	Detection of problems	
	Adjustment of antihypertensive medication	
Anxiety and stress	Compliance with antihypertensive medication	
	Personal	
	Relationships	
	Impacts on lifestyle	
Home blood pressure monitoring	Impact of blood pressure monitoring	
	HBPM advantages	
	HBPM concerns	
	Sharing HBPM readings with healthcare professionals	
	White coat effect	
	Voluntary HBPM	
Telemonitoring and self-management	Role of antenatal HBPM	
	Ease of use	
	Suggested improvements	
	Preference for / recommendation of self-management	

Within NVivo, case classifications were developed alongside the interviews and coding framework to determine whether participant characteristics influenced their views. These were based on demographic data collected at screening (age, ethnic origin, IMD quintile, body mass index (BMI) and parity); the details of a participant's HDP (diagnosis, gestation at diagnosis, gestation at delivery); and study details (recruitment site, allocation and withdrawal status). For the intervention group

information about compliance with and accuracy of HBPM, derived from the exploratory analyses (section 4.5.3.7) was also included.

Alongside the main qualitative analysis of the audio-recorded interviews, the coded responses to the interview questions were analysed using descriptive statistics. This dual approach aimed to bring out both 'articulated' data i.e. direct responses to the questions, as well as new 'emergent data'.

5.4 Results

5.4.1 Study participants

75/91 randomised women (82.4%) consented to participate in the qualitative sub-study. 34/38 (89.5%) from the intervention group and 34/37 (91.9%) from the control group completed at least one of the two audio-recorded interviews. In the intervention group 32/34 women completed two interviews, and 2/34 completed one interview. In the control group women 26/34 women completed two interviews, and 8/34 completed one interview.

Due to the total population sampling approach, a large number of interviews were performed, so secondary selection of which interviews to analyse was considered (section 5.2.3). However, after immersion in the data, through listening to the recordings, and reading the transcripts, it was decided that some important information would be lost by this approach, and so all interviews were transcribed and coded. 13/126 interviews (10%) were transcribed by the author, and 113/126 (90%) were transcribed professionally. The format of the transcribed interviews was standardised and these were uploaded into NVivo for coding and analysis.

The characteristics of the interviewees are displayed in the two study groups are displayed in Table 37 and Table 38, and demonstrate that a broad range of participants, from both the intervention and control groups, was interviewed.

Table 37: Baseline characteristics of interviewees from self-management group (n=34)

Interviewee ID*	Study site	Withdrawn	Age/y	Ethnicity	IMD quintile	Parity	Diagnosis	Gestation at delivery /weeks	% compliance (daily HBPM)	% accuracy (daily HBPM)
SM1	Oxford	No	37	Indian	4	2	PET	33.9	66.7%	94.4%
SM2	Oxford	No	31	White British	1	1	PET	36.6	64.7%	100.0%
SM3	Oxford	No	34	White British	3	0	PET	32.3	63.6%	90.9%
SM4	Oxford	No	34	White British	3	0	PET	38.3	100.0%	100.0%
SM5	Oxford	No	32	White British	2	0	GH	38.9	85.7%	96.9%
SM6	Oxford	No	36	White British	1	1	PET	37.0	80.0%	87.5%
SM7	Oxford	No	31	Pakistani	1	1	PET	36.3	61.1%	95.5%
SM8	Oxford	No	36	White British	2	0	PET	38.7	80.7%	94.1%
SM9	Oxford	No	34	White British	2	2	GH	39.1	44.4%	50.0%
SM10	Oxford	No	40	White British	2	0	GH	37.0	50.0%	100.0%
SM11	Oxford	No	34	White British	3	0	PET	38.0	90.0%	100.0%
SM12	Oxford	No	43	White other	1	1	GH	37.1	85.7%	57.1%
SM13	Oxford	No	28	White British	1	0	PET	38.0	100.0%	100.0%
SM14	Oxford	No	36	White British	3	3	GH	39.3	95.2%	100.0%
SM15	Oxford	No	26	White British	1	0	PET	36.4	92.3%	92.9%
SM16	Oxford	No	23	White British	1	0	PET	37.7	60.6%	28.6%
SM17	Oxford	No	31	White British	3	0	PET	37.9	100.0%	100.0%
SM18	Banbury	Yes	29	White British	3	0	GH	39.1		
SM19	Reading	No	35	White British	1	0	GH	40.6	100.0%	96.7%
SM20	Reading	No	29	White British	2	0	GH	37.1	100.0%	100.0%
SM21	Reading	No	29	White British	1	1	GH	38.1	38.9%	75.0%
SM22	Reading	No	26	White British	3	0	PET	36.0	43.2%	20.0%
SM23	Reading	No	28	White British	2	0	GH	37.4	98.4%	87.3%
SM24	Reading	No	34	White British	1	0	GH	40.9	93.0%	95.2%
SM25	Reading	No	28	White British	1	0	GH	40.0	73.9%	94.1%
SM26	Reading	No	39	White British	1	1	GH	39.9	90.9%	100.0%
SM27	Reading	No	31	White British	3	1	PET	39.3	100.0%	100.0%
SM28	Reading	No	25	White British	1	0	GH	40.7	85.7%	100.0%
SM29	Reading	No	39	White British	1	0	PET	30.0	98.5%	100.0%
SM30	Northampton	No	41	African	3	3	PET	32.1	74.1%	63.6%
SM31	Northampton	No	36	White British	4	0	GH	39.7	100.0%	90.9%
SM32	Aylesbury	No	29	White other	2	1	GH	37.6	79.1%	97.3%
SM33	Aylesbury	No	37	White British	4	0	PET	37.4	100.0%	90.0%
SM34	Aylesbury	No	25	White British	4	0	GH	39.4	100.0%	98.4%

Abbreviations: BMI = body mass index; GH = gestational hypertension; IMD = Index of Multiple Deprivation; PET = pre-eclampsia

* As referenced in the text; these have been changed from the ID numbers assigned during the study; prefix SM identifies women from the intervention group

Table 38: Baseline characteristics of interviewees from usual care group (n=34)

Interviewee ID [†]	Study site	Withdrawn	Age /y	Ethnicity	IMD quintile	Parity	Diagnosis	Gestation at delivery /weeks
UC1	Oxford	No	32	White British	1	1	PET	36.6
UC2	Oxford	No	36	White other	4	0	GH	40.0
UC3	Oxford	No	34	White other	5	1	PET	39.0
UC4	Oxford	Yes	25	White British	1	0	PET	29.0
UC5	Oxford	No	26	White other	2	0	GH	37.1
UC6	Oxford	Yes	34	White British	3	0	PET	36.6
UC7	Oxford	No	23	White British	3	0	PET	37.9
UC8	Oxford	No	32	White British	1	0	GH	37.1
UC9	Oxford	No	39	White British	2	0	GH	36.3
UC10	Oxford	No	36	White other	1	0	PET	37.4
UC11	Oxford	No	37	White British	1	0	GH	40.3
UC12	Oxford	No	31	White other	1	0	PET	27.9
UC13	Oxford	No	29	White British	3	1	PET	37.9
UC14	Oxford	No	35	White British	3	1	GH	40.3
UC15	Oxford	No	34	White British	1	1	PET	38.6
UC16	Oxford	No	30	African	3	3	PET	31.6
UC17	Oxford	No	31	White British	1	0	GH	39.9
UC18	Banbury	No	30	White British	1	0	GH	39.6
UC19	Reading	No	31	White British	2	1	PET	36.4
UC20	Reading	No	28	White British	1	1	PET	39.3
UC21	Reading	No	31	White British	1	0	GH	41.1
UC22	Reading	No	34	White British	1	0	PET	35.3
UC23	Reading	No	31	White British	4	0	GH	37.4
UC24	Reading	No	40	White British	1	0	GH	36.3
UC25	Reading	No	41	White British	1	1	GH	39.4
UC26	Reading	No	39	Asian other	2	0	GH	39.1
UC27	Reading	No	38	White British	1	2	GH	38.3
UC28	Reading	No	29	White British	4	0	PET	31.6
UC29	Reading	No	29	White British	2	2	GH	38.4
UC30	Reading	No	33	White other	2	1	PET	33.0
UC31	Reading	No	31	White British	1	0	GH	39.0
UC32	Northampton	No	28	White British	4	0	PET	35.0
UC33	Northampton	No	23	White British	3	0	PET	32.6
UC34	Northampton	No	23	White British	1	0	PET	37.4

Abbreviations: BMI = body mass index; GH = gestational hypertension; IMD = Index of Multiple Deprivation; PET = pre-eclampsia

[†] As referenced in the text; these have been changed from the ID numbers assigned during the study; prefix UC identifies women from the control group

5.4.2 Analysis of audio-recorded, free-text responses

From complete coding of the 126 interview transcripts according to the framework described above, several overarching themes emerged. Control over their condition was a major factor influencing participants' experiences of their healthcare. Time pressures were a key concern to women during this period, so ease of access to healthcare was critical. There was extensive discourse surrounding communication with healthcare practitioners, patient confidence, education and knowledge, as well as exploration of factors affecting stress and anxiety. Specific constraints to self-management were explored, as were participants' positive and negative experiences of the intervention.

Intriguingly 13/34 participants from the control group stated that they had used a home BP monitor at some stage, and many women from the control group unequivocally expressed a preference for HBPM (21/34, 61.8%). 11/34 did not comment, 1/34 reported she would prefer doctor-led care: "I felt more confident that they've done it, rather than if I was doing it myself" (UC25); and 1/34 had no particular preference: "I don't really have a preference... I've used BP monitors in the past so I would be happy with either" (UC25).

5.4.2.1 Control of condition

Participants frequently reflected that self-management enhanced how in control they felt of their condition: "A hundred percent [in control] yeah. Just doing it all the time so I can keep an eye on it" (SM29); "It means that actually I sort of always know where I stand with my blood pressure" (SM19); "With this study very in control, because I can check it every day, and then obviously act on that" (SM7). Several participants explicitly stated that self-management improved their level of control compared to BP management by health professionals: "when you're in hospital, or at the doctor's, and they take you straight in, you've lost control" (SM33); "every time I used to go to the doctors and come back and stuff I kind of didn't know where I was at; it kind of felt a bit out of control, and that definitely changed post-birth" (SM25).

Women felt that HBPM produced a more truthful picture of their actual BP: “it’s more accurate and you can do it at your own sort of leisure as well” (UC34). Participants in the intervention group noted that they liked the ability to check their BP if they developed symptoms: “if I felt like I was maybe feeling a bit funny or queasy or anything, I could just go and check and it was kind of that reassurance on myself” (SM25).

The views from the participants in the control group about their control of their condition were more inconsistent. Some were vocal that they lacked control: “I mean I am going in to get it checked, but I don’t feel that I have much control over what happens” (UC22) and “I just follow what the doctor tells me so it’s not that I control anything really” (UC12). Others felt that more information may have been helpful, “I mean apart from taking the tablets, I didn’t know what my blood pressure was. It might have been nice to be able to do that” (UC15). Some participants did report feeling in control, stemming from confidence in the care provided by their GP: “I’m mainly making decisions alongside the GP. I just get her agreement with it” (UC1). One participant specifically valued the input from a professional: “I felt more confident that they’ve done it, rather than if I was doing it myself” (UC10).

The explanations and information provided to women during their care (section 5.4.2.3) had a significant impact on their experience. In turn, their level of understanding seemed to correlate with the extent to which they felt in control of their condition: “last time and I felt far less confident about things. This time it’s more... I know about it before and so I kind of... it was easier to anticipate things” (SM12); “Yeah much more [in control], and I know much more about it myself” (SM22). Participants from the intervention group often reported that knowledge of their BP readings improved their understanding: “Being able to take my own readings and see what needs to happen. Rather than be dependent on waiting for other people” (SM26).

The extent to which participants felt they were sharing responsibility with their healthcare team was variable. Women in the intervention group did report sharing responsibility evenly with their GP: “I

think I've shared it quite a lot especially with taking the blood pressure myself, so I've taken some responsibility" (SM25) and "it felt like he [the GP] was kind of backing it that it's a good thing, you know to be involved in and you did it, and so yeah, no I was pleased" (SM22). Others from the intervention group acknowledged that they had often assumed a greater share of the responsibility, but did not in general view this as a negative consequence of self-management: "more onus is put on me, which I think's the right thing; I'm comfortable with it" (SM19). One woman from the intervention group reflected she might have liked more direct contact with a healthcare professional when adjusting her medication: "normally I'd be seeing a GP and could have discussions about stopping my medication" (SM9). However, this was an isolated view, and this participant had some conflicting views about her BP and her management, as she also said, "My GP has not had any input into anything so I haven't had to see him, and I was personally happy because my medication was taken away really quickly" (SM9).

Participants from the control group also reported variable levels of responsibility sharing. Some did not feel they had much input into their management: "I don't actually know what's constantly going on, just the fact that it's controlled by other people so... rather than myself... it's more been having someone else come in and do it, so you don't really share" (UC8); "they tell me how many to come down and I don't have a blood pressure machine, so I don't know if my blood pressure is raised or if it's low" (UC32). Others did feel like they played a greater role: "I could somehow... well not really maybe influence because you can't influence it as a patient, but still you are given the sensation you can participate in the whole thing" (UC2); "I think equally [sharing responsibility]... I think yeah we both... I mean both sides feel quite a good responsibility for this" (UC3). It is worth noting that the first of these patients reported undertaking HBPM during the study (section 5.4.2), and the second had access to an automated machine in the GP surgery (section 5.4.2.2).

Self-management afforded some women the belief that they were better able to detect issues with their BP: "I wouldn't have known it was low if I didn't have the monitor to do it myself, and then it

could have gone too low” (SM15); “I think that [HBPM] would actually have picked that up sooner. And I wouldn’t have had those dizzy spells necessarily” (UC18); “when my blood pressure dropped I was really surprised at how quickly it dropped and therefore how quickly my medication dropped... had I been going to see my GP, um, I’d actually been, I don’t, I don’t know what the risk levels are, but my blood pressure dropped so quickly that to have stayed on the maximum dosage of medication I think would have left me with quite worryingly low blood pressure, which then would have had its own side effects” (SM5).

Women in both groups discussed antihypertensive medication adjustment as a component of their control over their BP. Women in the intervention group frequently referred to the speed of the reduction of their doses in response to their BP readings. In general, this was perceived as a positive: “I think it made my medication be altered quicker, like the dose knocked down quicker than what it would if I’d gone and made doctor’s appointments” (SM15); “if I was going to the GP I would have waited two weeks and been on the full medication, and nobody really wants to be on medication if they don’t need to be” (SM31). Women perceived that HBPM enabled more appropriate, and often more rapid, down titration and cessation of antihypertensive medication: “looking at how fast my medications came down, surely if I was going to see a doctor I’d still be on it without really needing to be, because I wouldn’t be going” (SM13). One woman did express some concerns about the speed at which her medication reduced: “I think because of the monitoring that cut it down very quickly... I was almost reluctant to cut it down so quickly” (SM12) and another reported doing additional checks as the medication was decreased: “particularly when I had to reduce medication, just to check that it was holding on, so I checked at different times as well” (SM32).

Women in the control group relayed positive and negative experiences of postpartum medication adjustment: “I understand what is going on yeah with my blood pressure. And coming home, yeah it’s been monitored carefully and the medication reduced gradually, which I think stabilised my blood pressure” (UC16). Some women managed by their GPs did report concerns about the rate of

adjustment, in both directions: “perhaps I should have come off slightly earlier, but that was my fault being busy with a littleun” (UC23) and “They took me off it a bit suddenly I think. So, I think they took, took me off it too soon” (UC7). Another participant reported “I stopped taking the medication when it ran out” (UC33, control group). Participants in the control group also employed HBPM to guide medication adjustment: “I was also self-monitoring... I’ve called them [the GP] and said this is what my blood pressure’s doing, what, what should we do with the medication rather than waiting for an appointment” (UC9); “much more confident in changing the medication myself without asking a GP” (UC24). Participants in the control group did occasionally report strategies in which a usual model of care had been effectively adjusted in order to manage problems: “I’d been going dizzy and things like that... So I rang the doctor and he couldn’t see me that day but he said, ‘You can come in next week and in the meantime half what you’re taking’” (UC18).

5.4.2.2 Convenience: time pressures, access to healthcare and relationships with practitioners

Women in both groups explicitly referred to multiple competing time pressures, and cited this as a reason why they might prefer to self-manage: “It might be good to monitor it yourself because obviously with a baby it’s a bit of a pain sometimes having to go to the doctors and stuff” (UC17); “I just wouldn’t have found it good use of my time going to the doctor’s surgery” (SM26); “actually if I could have just sorted it out myself that would have made life a lot easier” (UC22). Women liked the flexibility that HBPM provided: “it’s been convenient to use it at home... I take it with me wherever I go; if I go away for a couple of days or something so yeah, so it’s really handy” (SM20); and felt that it saved them time relative to visiting the doctors’ surgery: “it saves time going to the doctors” (SM29); “And other ways it’s time saving... if I have to go to the hospital or GP just to check my... I have to do lots of arrangements” (SM1). These sentiments were shared by some women from the control group: “Self-management would definitely be better so you won’t have to have the hassle of going out all the time to see the GP” (UC7). One participant (SM29) who delivered extremely

prematurely, and whose baby spent a substantial time period on the neonatal intensive care unit, said, “It helped because it was just one less thing to worry about and one less appointment”.

New babies were frequently cited as restrictions on women’s availability and flexibility: “obviously it’s quite busy with two babies particularly” (SM6); “especially with a baby, it’s difficult to get both of us out of the house” (SM25); “I’ve got a new born baby and my routine’s all over the place” (SM20). Other women commented on the issues juggling other children and work commitments “it was hard work especially getting all four because it was the Easter holidays as well” (UC29); “Also if you’ve got a busy life with work and children, then it’s easy to do at home for sure” (UC13).

Access to care, specifically in relation to postpartum hypertension, was variable in both groups. Some participants reported that it was straightforward to get a GP appointment at their convenience: “My GPs are brilliant in the fact that they will book last minute appointments, and they will... they do cater for you” (UC29). Whereas another participant (UC22) recounted, “getting an appointment... my GP practice is slightly tricky, it seems a sort of dark art.” A similar scenario was found with regard to community midwife visits. One participant in the control group (UC15) stated: “I had no problem getting appointments. I was able to see a midwife on a Sunday as well, Easter Sunday, which you know I thought it would be a Monday to Friday.” In contrast to this, another participant from the control group (UC34) said, “the midwife said that she would come out and then no-one would turn up.”

Continuity emerged as an important factor influencing how women perceived the quality of care they received: “I try and see the same GP at the surgery and I think that helps with continuity, so they know what’s happened before” (UC27). Where participants achieved regular contact with their usual GP this experience was perceived as beneficial (UC12): “I think it was once a week I used to talk to the GP, and she used to... when I started going down in the medication she used to do it slowly do I didn’t have any problems, so good yeah.” Where continuity of care lapsed, women often reported issues with consultations: “I had an interesting experience with one slightly unhelpful duty

GP" (SM27). Other patients reported problems when changing GP surgeries: "Well I changed GPs. And then I've now gone back to my other one. Now I'm back with my other one it's much better" (UC31) and "I've got a new surgery and I don't feel happy going down there" (UC21). However, some participants did report a change of GP as beneficial: "I think it has helped me changing GPs and having a nice GP" (UC14).

The need for handover of care, and communication between different groups of healthcare professionals, were identified as potential issues influencing consistency of care. Participants reported some problems with inconsistency of message: "the community midwives completely ignored that and kept sending me back into hospital... to the point that the doctors in hospital said, '... we don't want to see you here unless your blood pressure's above 160 and 110.' They wrote that on my notes, and even so the community midwives kept trying to send me any time it was above 140 over 100" (SM32); "sometimes I have had conflicting information from midwife to GP to hospital" (SM26).

Participants' relationships with their healthcare providers affected patient care in many cases, with women frequently citing good relationships as one factor underpinning positive encounters: "I feel very confident, yeah they're so nice. Yes they're very helpful" (UC3) and "GP's not so bad now that I've got like a good one. He's a lot easier to talk to. So yeah alright, and he knows what's going on and everything as well so that helps" (UC31). However, there were some reports of poor relationships negatively impacting on care quality: "I need to go back for the blood pressure. They're not like my old surgery at all. So, I am trying... I suppose I'm trying to put it off a bit going. If it had been my old surgery I'd have had total confidence in them" (UC21).

Some women reported an active dislike of going to the doctors as a reason they would prefer to self-monitor: "I hate going to the doctors, and you can do it you know whenever you want at home; it's, you know it's so much easier" (SM29); "I hate going to the doctors... so with this I knew that I could make a phone call and say, 'Right, I've done this' and it was much more definite; it took a lot of the

unknown out of it, and took a lot of the stress out of it" (SM31). Several participants relayed suffering with white coat syndrome, and felt that HBPM was advantageous for them: "just the thought of going to the doctors would bring it up anyway" (SM8); "I found it useful just because it means I get a more accurate reading when I'm not stressed when I'm at home" (SM9). A number of participants highlighted that self-monitoring may reduce the burden on the NHS: "Big cost saving I think for the NHS really, and for time saving" (SM17).

Difficulties with travel to GP surgeries were reported as a barrier to accessing healthcare. Some women were unable to drive, sometimes as a result of delivery by caesarean section, resulting in them needing to rely on friends and family to provide transport: "because I don't drive, so I think it was better" (SM15) and "I've not been able to drive, actually go[ing] to the GP and have my blood pressure checked would just be a real faff" (SM17). Women may stay with family after giving birth, away from home and their usual GP, which can restrict their access to healthcare: "I think it's been convenient to use it at home for me personally because I wasn't at home; I was somewhere different from my GP's surgery so I was quite...away so it's fine, you know I take it with me wherever I go; if I go away for a couple of days or something so yeah, so it's really handy." (SM20). Other participants described difficulty in walking to appointments or sitting in waiting rooms following birth: "I mean going to the doctor's surgery would have been very difficult just with having a little one at the same time, having problems walking" (SM24); "Taking a new born sometimes you're in pain so you don't really want to walk..." (UC13); "it was really uncomfortable to sit for half an hour, so by the time I got upstairs, because I was waiting downstairs, my blood pressure was high" (SM33).

Participants from both groups reported a number of strategies employed by GP surgeries to improve access, including provision of an automated BP machine in reception, coupled with the facility to submit readings to GPs automatically: "they're good now at this machine in health centre, so I always can give a receipt from these to the reception, and they usually pass it straight away to GPs" (UC3). One participant (UC22) stated "I can also just go and do it; it only takes five minutes to go to a

pod", however did also acknowledge some difficulty with then communicating with her GP: "the only challenge was sometimes was that I would then have to try and arrange a phone consultation with my doctor, which sometimes took quite a few days to sort out." Several participants reported effective use of telephone consultations: "my doctor was quite good in that I'd phone her and say my blood pressure's doing this, and she'd adjust" (UC9). One participant explicitly mentioned the using email as a means to communicate with her GP: "a nice GP, who was happy for me to just email her rather than have to go in and see her" (UC14).

5.4.2.3 *Confidence, communication, education and knowledge*

In general, participants reported a high level of confidence when communicating with healthcare professionals: "I felt confident about talking to them about what was going to happen and I felt quite confident about negotiating with them" (SM4); "yeah confident with them and yeah, could be honest" (UC4). One theme, which emerged strongly from these data, was the impact of knowledge on women's confidence levels. Women from both groups articulated the bearing that both adequate and inadequate understanding had upon their conversations with healthcare professionals. Positive experiences included: "I think having the element of control and knowing what my blood pressure is, um, and learning a bit more about what blood pressure actually is and how it fluctuates during the day, and just having that information, um, it's made me feel more confident when I've actually had to speak to them about it" (SM5). In contrast, one participant related, "There's a way to educate and I didn't feel educated, and I think that made it more scary" (UC24).

The perception that they were being listened to substantially influenced participants' experiences of their interactions with healthcare professionals. Some participants reported very positive encounters: "a very good thing about her [the GP] was that she was really listening to what I was saying, and so my... I was thinking we were actually collaborating" (UC2); "I feel like I've got a say in... even with the GP he asked me if I'm happy to reduce it further. Yeah I felt I could discuss absolutely everything" (UC10); "They always take my thoughts into consideration" (SM2). Other experiences

were more variable: “I’ve swapped doctors so that’s made a big difference, and yeah they do listen more than my previous doctors” (SM22); “There was one occasion where I got... I think I got quite irate with a midwife because I felt she wasn’t listening to me, but all the other times were OK” (UC13). A number of participants reflected on negative episodes: “But them listening is a different story... I feel like it was me more talking and them just sort of ticking boxes, next person, to be honest” (UC34); “I found it a struggle to kind of have a normal conversation with somebody... I’ve spent a lot of time telling midwives and doctors that I have a massive anxiety which makes this much worse. I feel no-one ever listens” (SM9); “I can talk to my doctor about what I think I need, but he seems to overrule me” (UC32).

Women from the intervention group were explicit that specific knowledge of BP readings was helpful in this respect: “I have got control over seeing my readings, so I feel confident discussing them with them” (SM23); “very confident, but for me it helped that I had the numbers and knew what they were” (SM6); “Much more confident that I would have otherwise have been I think, because when they say, ‘Oh yes but how... you know how high has it been?’ or whatever and I can say, ‘Ooh well yesterday it was this and the day before it was that’” (SM27); “I didn’t have a clue what they were talking about before. So, now I know so much more of what is high, what is low, what is normal, especially for me” (SM22).

Women’s views of their GPs’ understanding of HDP varied. Some women felt GPs’ knowledge base was good, “I think they’re very knowledgeable actually” (SM34), whilst others expressed that they did not expect their GPs to be experts, for example, “GPs have different, uhhh, knowledge about things... they’re not specialists in everything so it’s hard for them to take confidence” (SM6). One participant acknowledged the difficulties GPs might face in adopting care from the hospital team: “especially if it’s a GP, because they... it’s not... you know the hospital controlled it all in and dealt with it all, and I think the GP would just say, ‘Well whatever they’ve said’, rather than you know taking the step to say, ‘Right, well let’s have a look and reduce it now and do this and that’” (SM7). In

contrast to these opinions, some women did convey concern about GPs' and midwives' knowledge: "sometimes it felt like they [the GP] were a little bit... they needed a bit of guidance themselves, the doctors" (UC17); "When I spoke to my GP about it I didn't really feel he had much awareness of it" (UC28); "I do think like my GP like, she's so lovely, but I think sometimes she doesn't really know; she's like asking me what I should be doing" (UC23).

During these interviews, how women accessed information about HDP was a recurring issue.

Women most frequently reflected on the information provided to them by their care teams, and the quality and content of these conversations was important. Women from both groups reported both enlightening and disappointing discourse with healthcare professionals about their condition, during pregnancy and postpartum. This is aptly illustrated by the following quote: "doctors in the hospital, I don't feel like it was ever really explained what the condition was... Going to [a postnatal service for discussion of birth experiences] was really good" (SM13). Another participant stated, "I don't think anybody really properly explained it to me" (UC24). However, these experiences contrast with some very positive reports: "I've discussed it a lot with other... a lot of health professionals, and I understand very much what's going on now compared to before" (UC16); "the midwives and doctors were very good at explaining things to me and giving me updates on where I was" (UC19); "I think she was [the midwife] was quite good about explaining in layman's terms" (SM27).

A small number of women reported being provided with some written information, either early in pregnancy, or following their diagnosis: "I've got the typical leaflet they give you, but because I didn't think that was going to happen to me I didn't read it" (UC12); "I've been reading leaflets and things" (SM15). One participant reported a pregnancy book as being a useful source of information, but highlighted the need for discussion with her care team: "I knew a bit from the pregnancy books, but it was definitely talking to the midwives that helps" (UC15). Women from both groups felt that additional information was provided to them as a result of enrolling in research, and seemed to believe this was beneficial: "I think if I hadn't have gone on one of the trials I might not have got as

much information... they had more time to actually talk about the conditions" (UC8); "reading through all of the information that the study's given me. That information that comes in that folder, that's been really good" (SM23). Some women from the intervention group explicitly referred to the BP threshold tables provided to them as part of the self-management (section 4.3.4) as a useful resource: "I liked the sheets of; you know that I was given of what's normal and what's not" (SM29); "I found the information sheet that I had would keep telling me what was high and, you know what was normal and low, so it was kind of helpful at sort of gauging if it was OK or not" (SM20).

Women who had suffered HDP in a previous pregnancy often quoted their past experiences as an important beneficial contributor to their understanding: "definitely better informed and yeah more manageable this time round" (UC1); "Because I've had pre-eclampsia before, and because it's reoccurred and I did the homework before I fell pregnant to prepare me" (UC20); "I had it last time so I know what the numbers should be roughly" (SM21). However, one woman clearly found that repeated experiences of gestational hypertension resulted in escalating stress: "I'd had it twice and bad experiences there that has brought me to this point of being very upset about it" (SM9).

Other sources of information recalled by women included other family members, television and the media. The personal experience of close female relatives clearly impacted on the women interviewed: "But I knew quite a bit about it before cos of my sister" (UC9); "I know from my mum's experience, but I never know from my experience" (UC26); "my mum's got high blood pressure so I feel like I could have... I'm speaking to her a lot more about her condition and comparing my notes and things like that" (04-033). One participant emphasised the potential risks from information in the media: "I think what is unhelpful is when you read stories in the media and things about people that have had pre-eclampsia, and you know the placenta failed and the baby died, and that's quite worrying" (SM17).

5.4.2.4 Concern

The impact, of HDP and their management, on women's personal anxiety and stress differed markedly between participants. Several women reported very little intrinsic anxiety, and very little effect from their condition and its management: "To be honest I didn't real have any anxiety about it" (SM25) and "Never really sort of had a, a massive fear of it anyway" (SM8). However, other women reported their BP problems resulting in significant anxiety: "I am an anxious person anyway, and I suffer with anxiety... And knowing it was high made me really concerned" (SM5); "it's quite a bit scary it, if I've been take medicine but my blood pressure still high" (UC26); "I'm quite a stressy person anyway to be honest, but it might have made me a bit more stressed" (UC23).

Similarly relationships with partners, existing children, other family and friends were affected in very disparate ways. A considerable number of women from both groups reported little or no negative effects, and several in fact reported strengthening of relationships: "it's more positive because we... everyone came together more especially with our friends here" (UC12); "everyone just comes together as well so it's not all negative; a lot of positives that comes from it as well" (UC33). Multiple women reflected that their partner had suffered considerable stress as a result of their condition: "my poor husband's been through the ringer... he's more stressed" (UC30). Women also acknowledged the impact of their condition on other children, "she's seen me get my blood pressure done, probably a bit too much for a four year old" (UC30), and other family members: "Mum always thought I was going to die" (SM15); "it did impact in the sense that I hid from everybody how far along I was, just to protect everybody else from the worry" (SM32).

Women did feel that HDP negatively impacted on their lifestyle: "it probably did impact probably my work, or working, and obviously a little bit on kind of home life because I wasn't able to do as much with my daughter, as much" (UC25) and "I would have to think about days out and who I was going to see for how long; where they lived" (UC20). This was often particularly the case before birth when they were admitted to hospital: "I didn't like being admitted to hospital" (UC9). Two women felt that

self-management had motivated them to pursue lifestyle changes to benefit their health: “actually I found it, um, really useful to be doing my blood pressure, because I um, it would make me think that I don’t want to eat that, or I don’t want to not go out, to my class or whatever” (SM5); “Yeah I think it’s [lifestyle] changed for the better; I’m more aware of what I eat, and exercising and looking after myself, and being more aware of my conditions I suppose” (SM3).

An existing concern expressed by healthcare professionals about self-monitoring is the possible capacity to increase patients’ anxiety about their health (318). With that in mind, women in the intervention group were directly asked about whether self-management influenced their anxiety. The majority of women categorically stated that self-management reduced their anxiety: “Because I had that I could take it and then contact somebody if my blood pressure was too high or too low, so it stopped me worrying” (SM15); “It was just great having the daily check; I think that made me really calm” (SM6); “It’s reduced my anxiety and put me back in control” (SM26). One participant revealed HBPM had helped her acclimatise to the sensation of having her BP measured, “I think as well it’s got me used to the feeling of the cuff and everything” (SM19). A small number of women reported little impact on their anxiety levels, as they were not worried anyway. Two patients reported potential for increased anxiety if their BP was high: “the first couple of days where there was a chance that I had to go back to hospital if it was high, it made me more anxious, but once it started coming down it made me less anxious” (SM13) and “Maybe if it was really high I might feel a bit anxious... I felt more relaxed because you let me monitor at home” (SM34).

One participant (SM9) held complex views of her BP management. On the one hand she reported, “just less going down for appointments...It’s very stressful when you’re like worried about your health and then you go somewhere”; “being able to do that if I felt it was going up at home, that’s really helpful” and “it decreased it [my anxiety] as in I didn’t have to drive all these children to the doctors and wait there... Saved me some stress”. However, in stark contrast to this she also found having a monitor at home stressful: “I think having a doctor there to reassure me makes it easier”

and “I had to have it [the monitor] sitting in my room looking at me, and I’m someone who hasn’t... just hates that”. This individual had clearly had challenging experiences as a consequence of her BP: “you just get more upset... my husband won’t even go in the [hospital name] anymore; like it’s caused a massive problem like in our family”. Another participant, who reported suffering with anxiety, provided an alternative perspective: “I’m really surprised. I thought actually there might be a big negative for me. Um but not no I don’t think it’s made me anxious, I think it’s, um, I think it’s done the opposite” (SM5).

Several women from the intervention group highlighted that self-management reduced their anxiety, relative to usual care from the GP: “going in to the doctors and things like that, yeah makes it worse for me... if they take it manually you don’t even know what it is; sometimes they don’t even tell you” (SM23); “I felt more relaxed because you let me monitor it at home. Had you made me go to the doctors, might have been a bit more worried perhaps” (SM34).

Participants from the control group were asked less directly about the impact of their BP management on their anxiety, due to the structure of the interviews. However, one participant did observe, “I think it [HBPM] would improve the anxiety yeah, because you’ve not got the pressure of someone looking at you at the same time, all sorts of reasons” (UC13). Some participants did comment on the impacts that the normal care structure had on them: “being told that someone’s coming out at some point today to come and like do something. So, you’re sat waiting in, nor doing something because you want to make sure that it’s OK... It was stressful to be honest” (UC34); “To put it bluntly, it was a bit of a faff” (UC29); “It’s been a bit tiring going; I think it was eventually every two weeks to check it” (UC30); “there’s no information given to me” (UC32).

5.4.2.5 Constraints

Women did report a few, often theoretical concerns, about HBPM. As outlined in section 5.4.2.4 one participant (SM9) had some variable views about self-monitoring, and stated, “it’s done on a text message so there’s no discussion I would say”. Two participants acknowledged that had they had

problems they would still have wanted direct contact with a healthcare professional: “I think if I found I had very, very strong symptoms and I wanted to speak to a GP I would... You know it would be better to go and have a chat with the GP” (SM20); “if I wasn’t feeling well I would probably want, every so often still someone anyway” (SM12). Another reflected on the importance of taking the BP correctly: “I think the only thing obviously is when you’re doing it yourself to make, you know are you sure you’re doing it right” (UC25).

Two participants highlighted specific practical difficulties with HBPM: “actually it’s very difficult to put a blood pressure cuff on yourself when there’s nobody else at home” (SM5); “if you’re not somebody that can... that hasn’t got support you might find it more difficult, because just finding the time to sit quietly to do your blood pressure can be tricky if you’ve got no-one there to hold the baby” (SM31). A handful of women from both groups recognised that whilst they might have preferred self-management, it might not suit everyone: “like a hypochondriac it’s better not to. So I think you need to analyse the patient before” (UC12); “some people do not want to [self-monitor] maybe, or some people are not able to” (UC2); “maybe other people may like the assurance of going to a doctor and them kind of confirming it to them” (SM25).

Participants encountered variable experiences when interacting with their healthcare professionals whilst self-monitoring. Some participants had very positive experiences, with GPs and midwives proactively asking about readings, and being happy for patients to take ownership: “when speaking to my GP about things, again the self-checking of that it gives them reassurance that you’ve got it rather than just being reliant on the appointments” (SM19). Others, however, thought their GPs felt rather uninvolved, and out of touch, “I think the only thing that’s come up a bit has been the GP finding it difficult; not feeling totally informed which was partly about me bringing the paperwork with me” (SM6); and some reported healthcare professionals not listening to them, or not trusting home readings, “the community midwives weren’t letting me do it; they were still doing it and sending it backwards and forwards into hospital” (SM32); “I think intrinsically they were a bit sort of

dubious about whether I could do it myself and whether I would be doing it accurately” (SM27). Two participants from the intervention group actually reported being allowed home from hospital early as a result of self-management: “initially when I was discharged from hospital I had to email my consultant my three readings a day. Because he let me come home early” (SM13); “if I didn’t do it I would have been in hospital a lot longer” (SM22).

5.4.2.6 Components of the intervention: participants’ experiences

Specific strengths of the self-management intervention, implemented in this trial, were identified by women, including the speed of response: “it’s been good getting the quick responses back” (SM6); “the text messaging is amazing because you get a response back straight away” (SM24). Women also reported that the system was clear when instructing them how to change their medication: “sorting out my medication when the text told me to and things like that, so I found that quite good” (SM4); “it was all on the messages on adjusting tablets” (SM28). Some women found the reminders helpful: “good I think, because I ain’t got the best memory, and they kept texting me to remind me” (SM15). Others described that, after moving to weekly readings, once they had stopped antihypertensive treatment, the automatic weekly medication confirmation checks served as a reminder: “the fact that I got the text in the week to check if I was still on any medication, meant that I’d go, ‘Ooh I haven’t done my blood pressure,’ and I’d do it, so yeah it fitted in with the fact I was busy” (SM31).

In general women found the telemonitoring services (the free SMS service and smartphone app) straightforward to setup and use: “Once I was shown how to use it properly I was away” (SM23); “they’re really easy to use; it was just the text message every day – really straightforward” (SM11). Some participants expressed a preference for the app: “they fit brilliantly but I would say... I’d say that the app is better because I like the way it says how you’re doing” (SM29). Participants also reported that the BP monitor was uncomplicated: “the machine’s straightforward” (SM21); “I think the cuff’s easy to use” (SM19).

Over the course of the trial a few isolated issues with the self-management did arise. Women reported some quirks with the app, which led to them being unable to read notifications without logging into the website: “alerts come through to say there’s messages, but I can’t actually see where the messages are” (SM17); “the app would often send me a, a message up, which would say you’ve got a new message, and I’d click it, and it’d take me to the app but I can’t read the messages on the app... so I had to go online to read any messages” (SM5). A small number of participants encountered difficulties with the pre-specified format of the SMS messages initially: “[at] the start, I didn’t notice the codes or... yeah but once that was... it was easy” (SM33); “Yeah a bit harder at the beginning... to get set up. There was a bit of confusion I think” (SM21); “I had difficulties at the beginning, but I didn’t do the space” (SM8). One participant was unable to submit readings using the SMS service as the 80*** number was blocked by her mobile provider, but had no problems using the app: “Yes [I had some problems with the text messaging service], but I can still send a text but with the app” (SM30).

During the interviews, participants made a number of suggestions about possible improvements to the telemonitoring system. The desired frequency of reminders was a common topic of discussion, and it was clear that women held different views about whether the addition of daily reminders would be beneficial, with some feeling strongly that they would: “Just having the reminders every day, rather than once in a while. Yeah, more text messages yeah” (SM7), whilst others would not want more frequent reminders: “because it was every sort of three days, so yeah, because otherwise you’ve gone too... yeah it would be nice to have it as an option but yeah not as a set thing” (SM22). It was apparent that some women also found that the reminders, and daily BP monitoring, served as a prompt for them to take their tablets: “Because I took so many tablets per day maybe like a reminder could have been something” (SM8). It emerged that perhaps the most sensible design would be to add the option for women to switch on (and off) daily reminders, to cater for this variation.

The weekly automatic medication checks the system employed, to ensure a medication change outside the down-titration schedule was not overlooked, were seen as a nuisance by some women, especially once antihypertensive treatment had ceased: “Just when it keeps saying, ‘Are you on any blood pressure medication?’. Because it asks you that about a thousand times” (SM29); “it kept asking me whether I had... you know about the medication, whether I was still on medication; so it kept asking me that and I was off for the whole time, so I thought that was maybe unnecessary” (SM12).

Whilst many participants felt the SMS service was easy to use, others raised that it would benefit from altering the structure of the messages to submit readings or respond to medication checks: “The text messages I definitely think could be better” (SM26). Some women liked the simplicity of the automated responses: “it’s [the response] it’s so clear about this is fine as long as you don’t have symptoms” (SM27). One participant felt that simply stating the blood pressure was satisfactory was insufficient: “I’m not sure if it gives enough information for people who might want to know, and it’s not the same as talking to a GP and them saying ‘Oh that’s absolutely fine. Someone came in earlier and theirs was much higher,’ you feel better, rather than just satisfactory” (SM9). One participant suggested email as an option for submitting readings: “Maybe email it rather than text messaging because I had a really bad habit of nearly forgetting to send text messages” (SM14), and she also recommended developing an online help resource: “you could do sort of like a Facebook pagey websithey thingy with like frequently asked questions on it”.

Participants very frequently stated that they would recommend self-management of BP postpartum to friends and family. One participant (SM1) in particular engaged in a very interesting discourse on this subject, highlighting what she perceived as a lack of awareness of self-management options and the associated support available (including discharging premature babies home with feeding tubes and self-management of gestational diabetes) amongst her culture: “Unawareness is the main thing. Like that, the same thing for the blood pressure control at home. Because if the main thing people

may think, 'Ooh is what happens?' Most of them are unaware and that will take all the... what we call the prejudice, it's all in my mind. But once it's been clearly known how to manage and things, all the clear instructions; once we've got it, it's really easy". She believed that sharing experience was critical to improving awareness and uptake: "I think they can talk to... if people like who had the same experience as... and they can convince them. Because if someone experienced will tell it was like this, not the other way".

5.4.3 Analysis of pre-coded numerical responses

Analyses of the numerically coded responses to the structured interview questions are presented in Table 39 and Table 40. The first part of the structured interviews was administered to both groups, and as such their responses could be compared over the trial period (Table 39). Five questions were asked, however data relating to the fifth question about the impact on relationships is not presented here, as it became apparent during analysis of the audio-recorded interviews that there was a systematic error by one of the two interviewers in how this question and answer scale was presented, such that some participants answered with a lower score implying more impact (as intended), but others with a higher score implying more impact (incorrect). The number of participants involved in this error was sufficient to invalidate the results.

Both groups showed a trend towards feeling more in control of their condition postpartum compared to screening (during pregnancy and pre-randomisation), and at both follow-up time points the intervention groups scored this question more highly than did the control group: adjusted difference at 4 weeks 0.6 (95% confidence interval 0.2 to 1.1); adjusted difference at 6 months 0.7 (95% confidence interval 0.3 to 1.2). For the remaining questions, concerning confidence in communication with healthcare professionals, responsibility sharing and knowledge levels, no significant difference was seen between groups. There seemed to be a tendency towards greater sharing of responsibility and knowledge postpartum, when comparing the screening scores to those obtained after birth (Table 39).

When evaluating the scores from the second half of the structured interviews (Table 40), which were administered only to the intervention group at the follow-up visits, the mean scores for these questions were high (all >4), suggesting that participants felt the trial intervention was generally well suited to managing their BP, straightforward to use and enhanced their lifestyle. In general participants were very positive that they would utilise self-management techniques in the future, and would recommend them to friends and family.

Table 39: Analysis of qualitative patient experience interviews (questions 1-4, both groups)*

	Screening Antenatal, pre-randomisation			Visit 2 4 weeks			Visit 5 6 months		
	<i>I</i> Mean (SD)	<i>C</i> Mean (SD)	Δ (<i>I</i> – <i>C</i>)	<i>I</i> Mean (SD)	<i>C</i> Mean (SD)	Adj. Δ (<i>I</i> – <i>C</i>) [†]	<i>I</i> Mean (SD)	<i>C</i> Mean (SD)	Adj. Δ (<i>I</i> – <i>C</i>) [§]
Number of responses	37	36	Mean (95% CI)	34	32	Mean (95% CI)	34	32	Mean (95% CI)
How much in control do you feel of managing your condition? [‡]	3.2 (1.2)	3.0 (1.4)	0.2 (-0.4 to 0.9)	4.6 (0.7)	4.0 (1.0)	0.6 (0.2 to 1.1)*	4.8 (0.7)	3.9 (1.1)	0.7 (0.3 to 1.2)*
How confident are you about taking an active part in the conversation when discussing your condition with health care professionals? [§]	4.5 (1.0)	4.6 (0.7)	-0.1 (-0.5 to 0.3)	4.6 (0.6)	4.5 (1.0)	0.1 (-0.2 to 0.4)	4.6 (0.8)	4.5 (0.8)	0.4 (0.0 – 0.7)
How much do you feel you are sharing responsibility of your treatment with a health professional? ^{**}	3.5 (1.4)	3.5 (1.3)	0.0 (-0.6 to 0.6)	4.1 (1.4)	4.1 (1.1)	0.0 (-0.7 to 0.7)	4.0 (1.3)	3.7 (1.4)	0.2 (-0.4 to 0.9)
How knowledgeable do you feel about your condition? ^{††}	3.4 (1.3)	3.5 (1.0)	-0.1 (-0.6 to 0.5)	4.1 (0.8)	3.8 (1.0)	0.2 (-0.2 to 0.6)	4.4 (0.7)	4.3 (0.9)	0.3 (-0.1 to 0.7)

Abbreviations: C = control; 95% CI = 95% confidence interval; I = intervention; SD = standard deviation

* Five questions were asked, however data relating to impact on relationships is not presented here, as there was a systematic error by one of the two interviewers in how this question and answer scale was presented.

[†] Adjusted difference between groups calculated using a mixed effects repeated measures regression model, adjusting for question score at screening and recruitment site

[‡] Scale: 1 (do not feel in control) – 5 (very much feel in control)

[§] Scale: 1 (not confident at all) – 5 (very confident)

^{**} Scale: 1 (do not feel that I am sharing responsibility) – 5 (very much feel that I am sharing responsibility)

^{††} Scale: 1 (do not feel knowledgeable) – 5 (feel very knowledgeable)

Table 40: Analysis of qualitative patient experience interviews (questions 6-10, intervention group)

	4 weeks Mean (SD)	6 months Mean (SD)
Number of responses	34	34
<i>The materials that you are using as part of the self-management: how well do you think they fit with managing your condition?*</i>	4.8 (0.4)	4.8 (0.5)
<i>How easy or difficult are you finding the self-management materials to operate?†</i>	4.9 (0.3)	4.9 (0.4)
<i>Have you seen a change in your lifestyle for better or for worse since starting self-management?‡</i>	4.1 (0.9)	4.4 (0.9)
<i>How likely are you to recommend the self-management of gestational hypertension / pre-eclampsia to friends, family and other people?§</i>	4.9 (0.3)	4.9 (0.4)
<i>How likely are you to use self-management approaches to manage medical conditions in the future?¶</i>	4.8 (0.6)	4.9 (0.4)

5.5 Discussion

5.5.1 Main findings

The key findings to emerge from these data were: [1] Largely women from the intervention group reported that HBPM and self-titration enhanced their feelings of control over their condition, and improved their anxiety related to their BP. The qualitative finding of improved control with self-management was supported by analysis of the coded quantitative data suggesting a significantly higher mean score in response to this question in the intervention group (Table 39). [2] A small number of participants reported anticipating that HBPM might increase their anxiety, but that in fact it had had the opposite effect. Only one participant interviewed reported that self-monitoring negatively impacted her, but at the same time did seem to perceive some advantages of HBPM. [3]

Abbreviations: SD = standard deviation

* Scale: 1 (do not fit with managing my condition) – 5 (fit very well with managing my condition)

† Scale: 1 (very difficult to operate) – 5 (very easy to operate)

‡ Scale: 1 (change in lifestyle for worse) – 5 (change in lifestyle for better)

§ Scale: 1 (not likely) – 5 (very likely)

¶ Scale: 1 (not likely) – 5 (very likely)

Women thought that self-management was more flexible, more reactive to problems and enabled more appropriate, and often faster, down-titration of antihypertensive medication. A putative theoretical model of factors positively and negatively influencing implementation and adoption of self-management in this trial is proposed in Figure 24.

Further reinforcing these views, women in the control group frequently undertook voluntary HBPM, and a majority of the control group expressed a preference for self-monitoring over usual care. A few potential concerns about HBPM were raised, including the importance of ensuring correct BP measurement, and that self-management might not suit everyone. However, these were expressed by a minority of women, from both groups, and were often theoretical in nature, rather problems encountered by women receiving the intervention.

When specifically considering the self-management intervention employed in the trial, women commonly reflected on its simplicity, clarity and ease of use. This was reinforced by high mean coded scores in response to questions in this section of the structured interview (Table 40). A few issues were identified, which were normally short-lived or resolved by the trial team. In particular these were problems with receiving notifications via the app, and some women initially having difficulties with the required structure of the SMS messages. These interview data produced some valuable suggested improvements to the telemonitoring service, which will be incorporated into the intervention when taking this forward. These suggestions included: optional daily reminders; modifying the system of medication consistency checks, especially once women have ceased antihypertensive treatment; optimising the structure of the SMS messages and wording of the automated responses; evaluating the role of an online help resource. Women in the intervention group found the reminder system helpful, with some suggesting it served as a prompt to take their medication, improving adherence. To this end the idea of medication reminders was also raised by some participants.

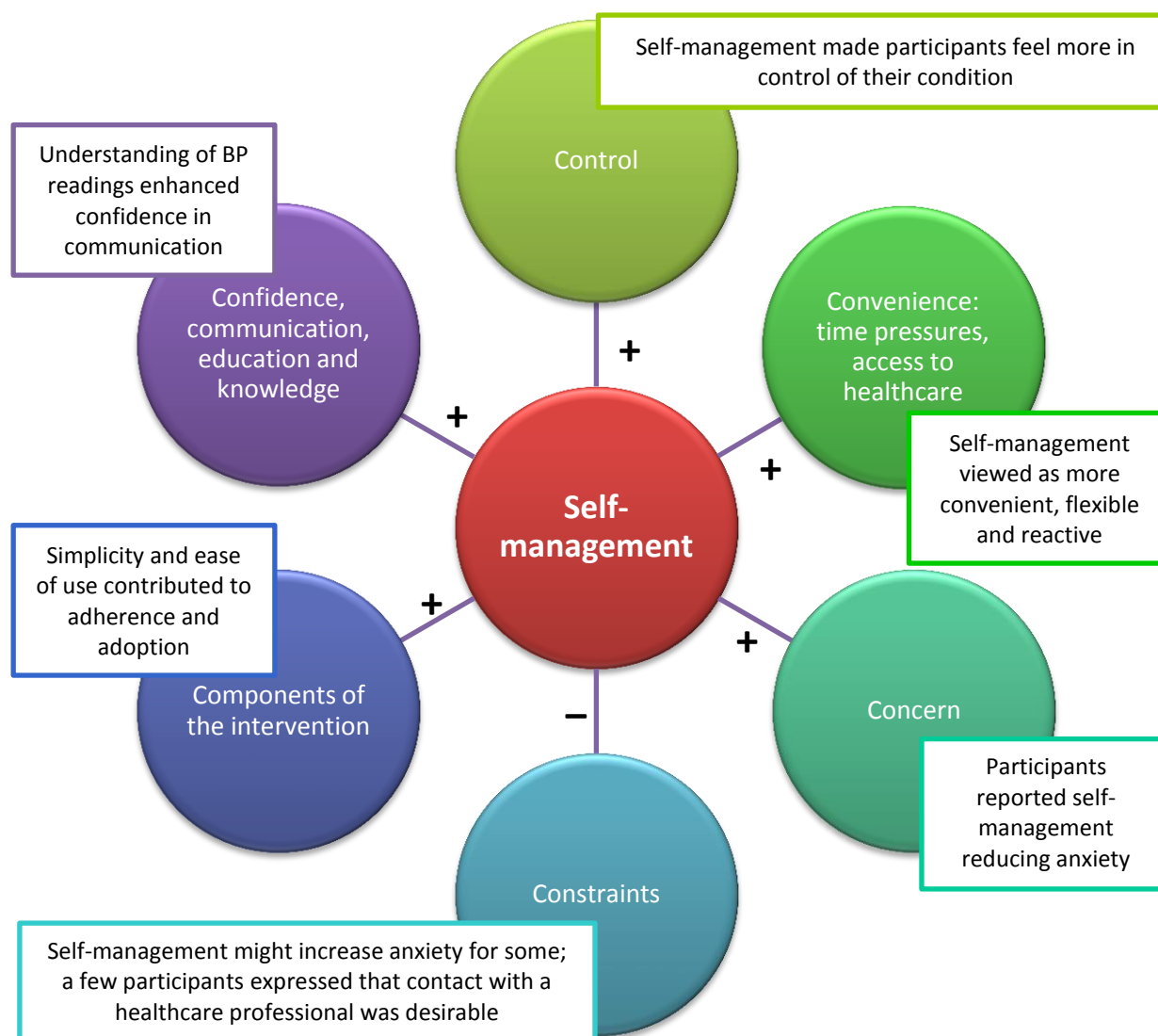


Figure 24: Proposed theoretical model illustrating factors influencing implementation & adoption of self-management for postnatal hypertension

In contrast to the fairly consistent views of self-management, women's experiences of doctor- and midwife-led care were rather more variable, perhaps reflecting the paucity of clinical guidance (section 1.7.3) and evidence (Chapter 2) that currently underpins postpartum hypertension management. Some participants reported extremely positive experiences of shared care, open communication, thorough explanations, easy access to healthcare and good continuity. Others encountered difficulty making appointments, inconsistent messages, particularly where continuity of care was lacking, and felt that their views were not listened to. How and where women retrieved information about HDP varied considerably across interviewees. Multiple sources of information were cited, most commonly discussions with healthcare professionals, and it was clear that the content and quality of these conversations impacted substantially on women's understanding and perception of the quality of their care.

This variation in care, also suggested by the survey results (Chapter 3), reinforces the need to establish a robust, comprehensive, patient-centred model of care for postpartum hypertension management. Previous work evaluating women's experiences of antenatal management of HDP has suggested an inadequate interface between community and secondary care (319). A survey exploring women's view of their maternity care in England (1995-2014) revealed a desire for increased support and contact with healthcare professionals during the postnatal period (320).

As might be expected, women from both groups relayed multiple competing time pressures postpartum, which influenced their views of their BP management. Their new baby, or babies, other children and work were all cited as commitments which impacted on their ability to access healthcare, and were common reasons women gave as to why they would prefer self-management, and why attending healthcare appointments was challenging.

5.5.2 Comparison to the published literature

Themes emerging from previous qualitative work evaluating BP self-management were echoed by this study: confidence with HBPM (279) and preference for self-monitoring (139, 297, 298). Patients

have previously reported HBPM to be more straightforward, time efficient and potentially more accurate in terms of representing their true BP (298). These themes were all reinforced by the findings reported here. Participants in this cohort seemed to report a higher level of confidence when down-titrating medication in response to readings, than has been reported in relation to up-titration of antihypertensive medications in poorly controlled essential hypertension (144, 279). The authors in that trial likened this behaviour to 'clinical inertia' amongst clinicians treating borderline readings, and it might be that participant motivation to stop treatment and not take tablets for longer than necessary alleviated this issue in the context of down- rather than up-titration.

Reclaiming and maintaining control over health have previously been identified as key consequences of self-management approaches in chronic illness, which act as positive facilitators to the implementation and sustainment of these interventions (321, 322). A systematic review of 22 qualitative studies examining self-management strategies in diabetes identified patient empowerment as a critical emerging theme (322). This was reiterated by a systematic review examining self-management strategies in chronic obstructive pulmonary disease, in which 'perceived control of worsening condition' emerged as an important positive factor in motivating patients (323).

Participants from a previous study, evaluating a mobile health intervention for chronic obstructive pulmonary disease, reported finding self-management reassuring, and becoming more aware of their condition as a consequence of the intervention (324). Both themes also emerged from these data, reinforcing the hypothesis that these may be factors, which encourage adoption of self-management techniques.

Some prior qualitative studies, examining barriers and facilitators to self-management approaches in patients with essential hypertension, have found substantial obstacles to self-management strategies, including distorted views of illness course, symptoms and treatment (325, 326). These were not identified in this study, which may reflect inherent differences between the population

with essential hypertension, and women with HDP, which in general have a limited time course. As hypothesised when considering this intervention (section 1.9.3), women may be more motivated, in the setting of a recent pregnancy, to take ownership of their health. A minority of women in this study did highlight the potential benefit of the regular contact with a healthcare professional encountered in usual care. This has previously been highlighted as an advantage of office blood pressure monitoring in a qualitative study evaluating patients' views of different BP monitoring modalities.

5.5.3 Variation in findings according to participant characteristics

During the analysis, no clear patterns emerged with regard to patient characteristics correlating with particular responses, and despite seeking differences through variation in the characteristics of the interviewees; responses were relatively consistent, especially with regard to self-management. These data suggest that the applicability and acceptability of this self-management intervention was not confined to a particular demographic. One aspect not considered was generalisability to other languages: at present, the intervention is only available in English, and so a future development may be to produce versions in other languages, to expand the population to whom it would be available if it were incorporated into clinical practice.

5.5.4 Strengths and weaknesses

This sub-study involved a large number of participants, evenly spread across the two study groups. The majority were interviewed at two time points, at four weeks and six months after birth. This meant that a broad range of opinions was sampled, and that the potential for evolution of participants' views over the study period was accounted for. The large population size also meant that the participants in the two groups were relatively diverse, covering a range of ethnicities, socioeconomic classes, parity and severity of diagnosis: pre-eclampsia versus gestational hypertension, and gestation at delivery (Table 37 and Table 38). During coding of the 126 transcripts

it became clear that saturation was achieved, as by the completion of coding no new themes emerged, and the coding framework no longer required adjustment.

One criticism of the study is that all the participants had consented to participation in a randomised trial of self-management, and therefore it is likely that they would be inherently biased towards a positive view of self-monitoring. However, it is worth noting that the recruitment rate into the main trial was high (59% of eligible participants approached), which may have limited this bias by ensuring the study sample was more representative of the whole population. Furthermore, due to resource limitation, members of the trial team, rather than independent researchers, conducted the interviews. It is therefore possible that participants may have felt pressurised to give positive responses regarding the self-management intervention. By adopting total population sampling, and thus interviewing a large proportion of participants (68/91 of those randomised), and including all transcripts in the analysis, it is hoped that the breadth of the opinions recorded limited this bias. The small number of participants who had low compliance with and poor accuracy of daily HBPM (section 4.5.3.7) were represented in the sub-study sample (Table 37), and therefore this should have allowed the views of those who found self-management more challenging to be heard.

5.6 Conclusions

These data provide considerable support for self-management of BP postpartum, and reinforce the effectiveness of the intervention developed for, and utilised in this pilot study. As suggested by the lack of research evidence (Chapter 2), limited clear national and international guidance (section 1.7.3) and considerable reported variation in care (Chapter 3), participants' experiences of postnatal BP management by GPs and midwives differed widely. In this cohort, self-management clearly enabled women to feel more in control of their healthcare, and reduced their anxiety. They perceived a self-led model of care as more flexible and better able to detect newly arising problems, as well as enabling more accurate, and targeted medication adjustment. Women generally felt comfortable measuring their own BP, and adjusting medication through telemonitoring, and

reported that the intervention designed for this trial was straightforward, fit for purpose and acceptable to patients. These data may help to shed light on the mechanism by which self-management was effective, in terms of improved BP control in this cohort, as they hint at improved adherence in the intervention group and more appropriately targeted titration of medication.

Chapter 6: Postnatal changes in markers of vascular risk in SNAP-HT participants: a sub-study

6.1 Objectives

Robust epidemiological data suggest that both gestational hypertension and pre-eclampsia are associated with future CVD in the mother (section 1.10), and importantly cardiovascular events seem to occur at a younger age in women with a history of pre-eclampsia (107, 327). Furthermore, a correlation has been shown between the risk of CVD and severity of HDP, with severe, early-onset pre-eclampsia conferring the greatest risk (105, 108, 328). A recent publication suggests that although a substantial component of the elevated risk of coronary artery disease, ischaemic and haemorrhagic stroke is accounted for by the correlation between hypertensive pregnancies and future essential hypertension, a still significant increased risk exists in women who are normotensive in middle age, suggesting a more complex relationship (110). It is unclear whether HDP unmask a predisposition towards developing CVD – with pregnancy acting as a ‘stress test’; or whether HDP inflict damage on a woman’s cardiovascular system, increasing the risk of developing CVD in later life (329).

Some evidence exists to suggest that the postnatal period may be important in this regard: in the HYPITAT trial, women who remained hypertensive at six weeks postpartum had a higher risk of being hypertensive 2.5 years postpartum (87). A further retrospective study indicated correlation between a higher BP six weeks postpartum and hypertension, six to 13 years later (111). It remains unclear whether the relationship between BP in the puerperium and hypertension in later life is solely driven by the severity of the underlying hypertensive disorder of pregnancy, or whether the quality of postnatal management, and the resulting BP control, has an impact. The SNAP-HT data suggest that self-management resulted in a reduction in DBP, which extended to six months postpartum (adjusted difference -4.5mmHg (95% confidence interval -8.1 to -0.8)), by which stage >95% were off treatment (section 4.5.3.4). The persistent reduction of DBP observed beyond treatment cessation, may reflect improved BP control influencing cardiac and/or vascular remodelling following pregnancy, resulting in beneficial changes in SVR or cardiac function. These

data suggest, for the first time, that better BP control during the puerperium could result in a lower BP in the medium-term, which, if it persists, may in turn modulate long-term cardiovascular risk.

No studies have demonstrated reduction of medium or long-term postpartum BP through different management strategies antepartum, including BP control. One previous trial (HYPITAT), evaluating induction of labour versus expectant management for gestational hypertension and mild pre-eclampsia, explored measures of cardiovascular risk two and half years postpartum. On average the induction of labour group had a seven day shorter antenatal period 'exposed' to hypertension but no difference was found in the cardiovascular risk profiles from the two groups (330). The CHIPS trial compared tight (DBP target 85mmHg) with less-tight (DBP target 100mmHg) control of BP during pregnancy in women with non-proteinuric gestational or pre-existing hypertension. No difference was found in their primary composite outcome (pregnancy loss or high-level neonatal care for more than 48 hours during the first 28 postnatal days) or overall serious maternal complications, although the tight-control group was significantly less likely to develop severe hypertension ($\geq 160/110$ mmHg) (275). To date, no long-term follow-up has been published.

If BP control is indeed shown to be relevant, one plausible explanation for the influence postpartum control may exert over long-term cardiovascular risk, is the notion of duration of exposure. The results from SNAP-HT (section 4.5.3.4) suggest women spend proportionally more time with treated hypertension postpartum than they do during pregnancy: across the whole study population the mean antenatal duration of treatment was 15.2 days (Table 22), versus a mean postnatal duration of treatment 44.2 days (Table 32). Achieving better postnatal BP control could impact on long-term risk, as a function of exposed time.

An embedded sub-study was conducted during the SNAP-HT trial (Chapter 4) to analyse markers of vascular risk in women from both study groups. This was designed to evaluate appropriate methodologies and assess the feasibility of incorporating such a study into a trial on a larger scale in the future. The baseline characteristics of the two treatment groups were expected to be similar, so

if a treatment effect from the intervention was demonstrated, in terms of BP control, this would allow further exploration of the relationship between BP control in the postnatal period and markers of vascular risk.

6.2 Background

6.2.1 Hypertensive disorders of pregnancy and long-term cardiovascular risk: potential mechanisms

Identification and understanding of potential pathophysiological or molecular links between HDP and CVD are important as they may provide ways to comprehend and measure therapeutic impact on long-term vascular dysfunction, and could potentially provide new therapeutic targets (331). The pathophysiology of hypertensive disorders is complex and inadequately understood (section 1.6). It is clear that they are placenta-mediated conditions (35), and elevated BP is believed to result from vasoconstriction and increased SVR (36), mediated by alterations in the circulating concentrations of vasoactive mediators. In pre-eclampsia, it is hypothesised that deficient placentation results in chronic placental ischaemia, leading to the release of reactive oxygen species and cytokines, producing an exaggerated systemic inflammatory reaction (332).

Evidence also exists that in pre-eclampsia the response of the vascular endothelium to both endogenous and exogenous vasopressors is altered in HDP (37). The vascular endothelium plays a central and complex role, as both a mediator and target, in all CVD (333). Changes in endothelial function occur early in disease processes, and abnormalities may be identified before disease is clinically evident (333). Endothelial dysfunction in HDP has been shown to persist postpartum. Endothelium-dependent dilatation (brachial artery flow-mediated dilatation) was lower in women with previous pre-eclampsia (n=113) than healthy controls (n=48) at a median of 3 years postpartum, whereas no difference was seen in endothelium-independent dilatation (glyceryl trinitrate-induced dilatation) (334). This result was echoed in a more recent study involving women

with gestational hypertension: endothelium-dependent dilatation was found to be impaired 20 months after a pregnancy complicated by gestational hypertension (n=15), compared with healthy controls (n=15). As before, endothelium-independent vasodilatation was comparable in the two groups (109).

These observations are supported by data on a macroscopic level: the rise in SVR, resulting from reduced total arterial compliance and increased proximal arterial stiffness, seen during pregnancies complicated by hypertension (36, 335, 336), has been shown to persist postpartum, for up to three years (296, 337).

Structural and functional cardiac changes, including left ventricular hypertrophy and diastolic dysfunction, are well-documented in women with HDP (338-340). It has been proposed that the increase in left ventricular mass indices represents an adaptive response to the amplified SVR (338). Despite earlier data suggesting resolution of cardiac changes by four weeks postpartum (341), more recent data have consistently demonstrated that the cardiac changes persist following hypertensive pregnancies (294, 295, 342-345). A prospective case-control study reported a higher incidence of diastolic dysfunction, and impaired myocardial relaxation in women with a history of pre-eclampsia, up to two years postpartum (294). Retrospective data have been published suggesting a higher incidence of diastolic dysfunction, up to 20 years after a hypertensive pregnancy, when compared to women with a history of normotensive pregnancy. The cohort exposed to hypertension during pregnancy also had a higher incidence of left ventricular hypertrophy, but this difference was negated by adjusting for duration of essential hypertension, suggesting that the relationship may result from an elevated risk of essential hypertension, rather than remodelling as a direct consequence of a hypertensive pregnancy (344). An emerging concept across these studies is that they often demonstrate persistent diastolic, but not systolic, dysfunction (295, 337, 344).

6.2.2 Vascular dysfunction measures

Arterial stiffness is now accepted as an independent prognostic marker in CVD (346, 347), and has been found to be increased in HDP (section 6.2.1), both during pregnancy (335) and postpartum (337). Arterial stiffness is a dynamic property dependent on the interaction of multiple variables, including arterial pressure, in addition to vascular structure and function, which also varies across the vascular tree. Arterial pressure in turn can be increased by elevations in heart rate, an amplified stroke volume and increased vascular resistance. These factors make it clear that a standardised approach to measurement is required (348). The measurement of carotid-femoral pulse wave velocity (PWV) is the simplest, non-invasive, robust and reproducible method to measure arterial stiffness and is considered most valid as it directly measures PWV along the aorta, and aorto-iliac tree (349).

The arterial pulse waveform can also be used to assess arterial stiffness. Two distinct peaks are seen within this waveform: the first from direct transmission of the pressure resulting from contraction of the heart during systole, and the second resulting from reflection of the pressure wave by the narrower, more resistant arterioles. The stiffer an artery is, the faster the wave is both transmitted and reflected back, and by calculating the timing of the reflected wave a measure of 'augmentation' can be derived (350). Evidence exists to support the validity and reproducibility of the measure of augmentation index (Aix) (351).

However, both PWV and Aix can differ with physiological changes in BP and pulse rate. More recently a novel arterial stiffness measure has been proposed: the cardio-ankle vascular index (CAVI) provides a global measure of the arterial stiffness from the origin of the aorta via the femoral artery to the tibial artery that is independent of BP at time of measurement. The distance from the level of the aortic valve to the measuring level (the ankle) is recorded and the time delay between the closing of the aortic valve (second heart sound) to the detected change in arterial pressure wave at the set point (352-356). However, the evidence base for arterial stiffness as measured by CAVI and

cardiovascular risk is substantially less well-developed than that for PWV, although correlation with more established markers of cardiovascular risk has been demonstrated (357).

6.2.3 Biomarkers in pre-eclampsia

Significant research attention has been focussed upon the potential molecular link between placental ischaemia and the systemic manifestations of HDP. As previously discussed (section 1.6) the anti-angiogenic sFlt-1 and angiogenic PlGF seem to be the most promising in terms of prediction and prognostication in pre-eclampsia (68, 69, 72) and have also been associated with cardiovascular features of the condition. The sFlt-1:PlGF ratio has been suggested as an adjunctive diagnostic test for pre-eclampsia (74), as it is known that the circulating levels change in advance of any clinical manifestation of pre-eclampsia (72, 75). A recent observational study has developed a validated sFlt-1:PlGF ratio predictive cut-off for use in pre-eclampsia diagnosis (76), which also correlates with interval to delivery (358). An economic evaluation of the test has been published suggesting cost-saving, through reduction of unnecessary hospital admissions (359). An RCT has recently been completed, but not yet published, evaluating the utility of this measure as a supplement to routine clinical practice (360).

In May 2016 NICE approved the use of two tests (Triage PlGF tests (Alere International) and Elecsys immunoassay sFlt-1/PlGF ratio (Roche Diagnostics)) to help rule-out pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation, however, due to cost considerations, these have not yet been widely implemented. NICE acknowledge that both the tests show promise in helping to rule-in pre-eclampsia, but stated there was insufficient evidence to support routine adoption in the NHS (361).

These angiogenic pathways also have the potential to yield therapeutic targets, and some recent research studies have focussed on depletion of antiangiogenic factors (via apheresis) or promotion of angiogenic factors (PlGF through administration of statins) during pregnancy to treat severe pre-eclampsia (362, 363).

Vascular endothelial growth factor (VEGF) is involved in the assembly of primordial vessels, initiation and regulation of angiogenesis (364), and is produced by the placenta (68). It has been shown to be depressed in patients with pre-eclampsia, and a recent systematic review listed it as one of the most promising markers of pre-eclampsia (68). Soluble endoglin (sEng) is an antiangiogenic marker, which like sFlt-1 has been seen to rise in women with pre-eclampsia, correlates with disease severity and regresses after delivery (365), and it has been proposed that this factor interacts with sFlt-1 in the pathogenesis of the maternal syndrome of pre-eclampsia (366). So, whilst VEGF and sEng have not been approved by NICE for use in routine clinical practice the decision was taken to include these markers in these analyses.

6.3 Methods

6.3.1 Sub-study participants

The intention was to recruit a minimum of 15 women from each treatment group (total 30 participants) in the SNAP-HT trial into this sub-study. No further eligibility restrictions were imposed beyond those for the main trial (section 4.5.2.2). Women were provided with information about this sub-study as part of the main participant information sheet (section 4.4.1.2), and signed a separate section of the informed consent form at their screening visit.

6.3.2 Sub-study design

Women consented to an extended visit at either baseline or the first follow-up visit at day 10 (day 1-14 postpartum) and again at 12 weeks, which took place at the Cardiovascular Clinical Research Facility, John Radcliffe Hospital (Oxford). At these visits, measures of arterial stiffness and capillary density were performed, and a blood sample was taken to measure circulating biomarkers relevant to cardiovascular health and HDP.

6.3.2.1 Arterial stiffness

The CAVI was measured using VaSera VS-1500 (Fukuda Denshi Co. Ltd, Tokyo, Japan) to give a global assessment of arterial stiffness, independent of BP. This involved placing BP cuffs on both upper arms and ankles, with electrocardiogram and cardiac phonogram monitoring.

The carotid-femoral PWV was measured using applanation tonometry, with three-lead electrocardiogram monitoring, to obtain sequential pressure waveforms of the right common carotid and right femoral pulse (SphygmoCor; AtCor Medical, West Ryde, NSW, Australia). The PWV is derived from recordings of the time delay between the two sites of measurement calculated from the R-wave of the electrocardiogram, relative to the distance between them (measured from the sternal notch). The aortic BP and AIx were measured from the pressure waveforms of the radial pulse obtained by applanation tonometry adjusted to a mean heart rate of 75 beats per minute (SphygmoCor; AtCor Medical). This was calibrated using the brachial arterial SBP and DBP measured with an automated oscillometric monitor, validated in pregnancy and pre-eclampsia (Microlife WatchBP® Home) (128).

All measures were conducted with participants lying flat, and participants did not speak or sleep during measurements. Participants had abstained from alcohol for at least 10 hours before measurement (349).

6.3.2.2 Blood samples

Investigators took a 40ml blood sample with the patient fasted (ideally a minimum of six hours clear fluid only) to measure circulating biomarkers relevant to cardiovascular health. Samples were stored at -80°C in facilities within the Department of Cardiovascular Medicine. Standard analyses were performed in batches by laboratories in the University of Oxford, John Radcliffe Hospital. Novel analyses were performed by the author. With the explicit consent of participants for the gifting of samples, samples will be transferred to a tissue bank for future use.

Standard pre-eclampsia blood results (blood counts, renal and liver function), lipid profile and glucose homeostasis (assessed by fasting insulin, glucose and Homeostasis Model Assessment (HOMA)) were measured by standard techniques.

Novel proposed biomarkers (sFlt-1, PlGF, VEGF and sEng) were analysed using Quantikine® enzyme-linked immunosorbent assays (ELISA), R&D Systems®. These employ the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific to the biomarker was pre-coated onto the microplate. During analysis, samples and standards were pipetted into the wells, and the immobilised antibody bound any biomarker present during an incubation period. The plates were washed to remove any unbound substances, and an enzyme-linked polyclonal antibody specific for the biomarker was added to the wells. The plates were incubated and then washed to remove any unbound antibody-enzyme reagent, before a substrate solution was added. This substrate solution developed colour in proportion to the amount of biomarker bound in the initial step. After a pre-prescribed time-period a solution was added to stop colour development, and plates were read using a microplate reader set to 450nm, with wavelength correction of 570nm.

6.3.3 Sub-study statistical analysis

CAVI, aortic BP, Aix, PWV and circulating biomarker data (routine pre-eclampsia blood tests and novel proposed markers) were analysed by presenting the mean and standard deviation by treatment group. The raw differences in the means were presented at both baseline and 12-week postpartum follow-up, with 95% confidence intervals. For the continuous outcomes at follow-up (12 weeks) a linear regression model was fitted, with treatment group as the independent variable and adjusting for baseline results. Adjusted differences were presented with 95% confidence intervals. P values were not reported as this study was not powered for the measured outcomes.

The measures were also compared for the whole study population between baseline and 12 weeks. Paired two-sample t-tests were used for these analyses, and raw mean differences reported with 95% confidence intervals.

6.4 Results

6.4.1 Sub-study participants

Table 41: Baseline characteristics of vascular risk sub-study participants (n=16)*

	Intervention (I) (n = 10)	Intervention (I) (n = 45)	Control (C) (n = 6)	Control (C) (n = 46)
Mean age (SD) /years	32.2 (5.1)	31.7 (5.3)	31.0 (4.5)	31.7 (5.3)
Mean BMI (SD) /kg/m²	31.4 (5.6)	29.0 (7.5)	26.2 (6.4)	28.0 (8.3)
Parity (frequency (%))				
0	7 (70%)	32 (71%)	4 (67%)	31 (67%)
>=1	3 (30%)	13 (29%)	2 (33%)	15 (33%)
Ethnicity (frequency (%))				
White (British)	9 (90%)	38 (84%)	3 (50%)	37 (80%)
Other	1 (10%)	7 (16%)	3 (50%)	9 (20%)
IMD quintile (frequency (%))				
1 st	4 (40%)	16 (36%)	4 (67%)	22 (48%)
2 nd + 3 rd	4 (40%)	23 (51%)	0 (0%)	16 (35%)
4 th + 5 th	2 (20%)	6 (13%)	2 (33%)	8 (17%)
Diagnosis (frequency (%))				
Gestational hypertension	5 (50%)	20 (44%)	2 (33%)	22 (48%)
Pre-eclampsia	5 (50%)	25 (56%)	4 (67%)	24 (52%)
Median PCR (IQR) (if PET)	141 (52.3 to 205.2)	109.2 (55 to 152.9)	64.25 (35.5 to 121.8)	55.4 (41.4 to 114.5)
Median gestation at diagnosis (IQR) / weeks	36.7 (31.6 to 38.7)	35.9 (31.9 to 37.7)	36.1 (34.7 to 36.6)	34.7 (31.7 to 36.9)
Median gestation at delivery (IQR) / weeks	38.1 (36.6 to 39.9)	37.6 (36.2 to 39.2)	38.2 (36.6 to 39.6)	37.2 (36.3 to 39.1)
Median duration of AN AHT treatment (IQR) / days	4.5 (1 to 11)	10 (4 to 19)	14.5 (12 to 19)	9 (5 to 22)
Median amount of AHT treatment at baseline visit (IQR) (WHO DDD)	0.7 (0.3 to 1.3)	1 (0.7 to 1.5)	0.8 (0.7 to 2)	1 (0.7 to 1.7)
Mean SBP /DBP at booking visit[†] (SD) / mmHg	114.3 / 73.1 (7.8 / 6.9)	119.2 / 72.7 (14.1 / 9.3)	112.8 / 73.8 (11.7 / 9.8)	116.8 / 73.0 (12.6 / 9.4) [‡]
Mean SBP / DBP (readings 2+3) at baseline[§] visit (SD) / mmHg	128.8 / 83.4 (11.6 / 6.8)	135.2 / 87.1 (15.5 / 9.2)	125.5 / 83.0 (12.1 / 12.9)	130.8 / 85.4 (13.0 / 10.5)

Abbreviations: AHT = antihypertensive; AN = antenatal; BMI = body mass index; C = control; DBP = diastolic blood pressure; I = intervention; IMD = Index of multiple deprivation; IQR = interquartile range; MAP = mean arterial pressure; SBP = systolic blood pressure; SD = standard deviation

* Characteristics of whole randomised population (n=91) included for comparison

[†] The booking visit usually takes place in the first trimester (before 12 weeks)

[‡] n = 44 as missing data for 2 participants

[§] The baseline visit is visit 2, and takes place day 1 – 6 after birth

41/101 (41%) participants consented to inclusion in this sub-study during the initial consent process. 4/41 withdrew from the entire trial pre-randomisation, and a further 21/37 (14 intervention, 7 control) withdrew from the vascular risk sub-study prior to the baseline visit. 16/37 (10 intervention, 6 control) attended the vascular risk sub-study baseline visit. 11/37 (8 intervention, 3 control) attended the follow-up visit at 12 weeks.

The characteristics of the 16 women who attended their vascular risk sub-study baseline visit are presented in Table 41. The two groups were broadly similar, but slightly more variation was observed than when evaluating the whole study population (Table 22), as might be expected given the much smaller sample size. The differences observed between the groups may have impacted on the results from this sub-study. The control group contained a greater proportion of women with pre-eclampsia (67% versus 50%), but the median urinary PCR in the intervention group was higher (141 versus 64), potentially suggestive of more severe pre-eclampsia in this group. The control group had a more diverse ethnic mix, a lower mean BMI and a longer duration of antenatal antihypertensive treatment.

6.4.2 Arterial stiffness

No significant differences were seen in the CAVI, PWV, Alx (adjusted to heart rate 75) or aortic BP at baseline or follow-up between the groups (Table 42). The usefulness of the PWV and pulse wave analysis data were limited by some technical difficulties measuring these parameters, especially in women with raised BMI, and a period during the study when the equipment was broken (June to August 2015), restricting the number of observations even further at both visits.

All participants who attended study visits had their CAVI measured at baseline (n=16) and follow-up (n=11). Mean CAVI was compared at baseline versus 12 weeks for the population with data available at both time points (n=11): the unadjusted mean difference was -0.3 (95% confidence interval -0.9 to 0.2), suggesting a non-significant trend towards a lower arterial stiffness as women recovered from HDP. The same comparison between time points was done for PWV which showed no significant

difference between the two time points. Mean PWV was 6.4 ms^{-1} (SD 1.0) at baseline (n=12) and 6.0 ms^{-1} (SD 0.9) at 12 weeks (n=7). The unadjusted mean difference for the population with data available at both time points (n=4) was 0.03 ms^{-1} (95% confidence interval -1.2 to 1.2).

The mean aortic BP also fell from baseline to 12 weeks, but again this was non-significant: 118.4mmHg (SD 10.1)/83.9mmHg (SD 17.1) at baseline (n=15), versus 115mmHg (SD 15)/81.9mmHg (SD 10.0) at 12 weeks (n=8). The unadjusted mean difference for the population with data available at both time points (n=7) was -2.4mmHg (95% confidence interval -12.0 to 7.1)/-5.3mmHg (95% confidence interval -11.1 to 0.6). However, when the mean Alx (adjusted for heart rate 75) was also compared over time, this did not show a reduction; in fact the tendency was towards an increase between the two time points: 18.1% (SD 7.7) at baseline (n=15), versus 23.6% (SD 10.3) at 12 weeks (n=8). The unadjusted mean difference for the population with data available at both time points (n=7) was 4.3% (95% confidence interval -5.9 to 14.5).

Table 42: Markers of arterial stiffness

	Baseline / Visit 1 (PN day 1-14)			Visit 4 (PN day 77-91)			
	Intervention Mean (SD)	Control Mean (SD)	Δ (I-C) [*] (95% CI)	Intervention Mean (SD)	Control Mean (SD)	Δ (I-C) [†] (95% CI)	Adj. Δ (I-C) [‡] (95% CI)
Cardio-ankle vascular index (CAVI)							
<i>Number of observations</i>	10	6		8	3		
Right CAVI	6.7 (0.7)	6.9 (0.5)	-0.1 (-0.8 to 0.6)	6.4 (0.7)	6.4 (0.6)	-0.0 (-1.0 to 1.0)	-0.0 (-1 to 1.1)
Left CAVI	6.6 (0.6)	6.7 (0.8)	-0.1 (0.9 to 0.6)	6.5 (0.6)	6.6 (0.6)	-0.2 (-1.1 to 0.7)	-0.2 (-1.2 to 0.8)
Mean CAVI	6.7 (0.6)	6.8 (0.6)	-0.1 (-0.8 to 0.6)	6.4 (0.6)	6.5 (0.6)	-0.1 (-1.1 to 0.9)	-0.1 (-1.1 to 0.9)
SphygmoCor: Pulse wave analysis							
<i>Number of observations</i>	9	6		7	1		
Aortic SBP / mmHg	118.1 (11.1)	118.8 (9.5)	-0.7 (-12.7 to 11.2)	116.4 (15.6)	105 (.)	11.4 (-29.5 to 52.3)	9.7 (-25.1 to 44.4)
Aortic DBP / mmHg	81.4 (21.8)	87.7 (5.3)	-6.2 (-26.1 to 13.6)	82.9 (10.4)	75 (.)	7.9 (-19.4 to 35.1)	5.0 (-16.6 to 26.6)
Alx (@ HR 75) / %	16.8 (8.8)	20.0 (6.1)	-3.2 (-12.4 to 5.7)	25.6 (9.4)	10.0 (.)	15.6 (-9.1 to 40.2)	15.2 (-16.7 to 47.2)
Sphygmocor: Pulse wave velocity (PWV)							
<i>Number of observations</i>	8	4		6	1		
PWV / ms ⁻¹	6.6 (1.0)	6.0 (1.1)	0.6 (-0.8 to 2.0)	6.2 (0.7)	4.7 (.)	1.5 (-0.4 to 3.4)	[§]

Abbreviations: C = control; CAVI = cardio-ankle vascular index; CI = confidence interval; HR = heart rate; I = intervention; PN= postnatal; PWV = pulse wave velocity; SD = standard deviation

^{*} Raw difference between groups presented for baseline data

Abbreviations: HR = heart rate; PN= postnatal;

[†] Raw difference between groups for follow-up data

[‡] Adjusted difference calculated using linear regression model, adjusting for baseline result

[§] Unable to perform linear regression as the single participant in control group at follow-up had not contributed baseline data for this measurement

6.4.3 Serum analyses

No significant raw or adjusted differences were seen in any of the measured routine biochemical markers of the end-organ complications of pre-eclampsia, conventional biochemical markers of cardiovascular risk or novel angiogenic and antiangiogenic factors (Table 43). Non-significant differences were noted between the groups at baseline, with the control group having higher sFlt-1 and sEng levels, and lower PlGF and VEGF levels, suggestive of potentially more severe pathology in the control group.

All the novel serum markers fell between the baseline visit and three months postpartum (Table 44). For the antiangiogenic factors sFlt1 and sEng the 95% confidence intervals around the unadjusted differences did not cross zero.

The urea values actually rose between baseline and 12 weeks for the whole population, although the difference was non-significant: 3.9mmol/L (1.2), versus 4.8mmol/L (1.0). The unadjusted mean difference for the population with data available at both time points (n=11) was 0.7mmol/L (95% confidence interval -0.4 to 1.8). For the whole population the mean uric acid level fell significantly between baseline and 12 weeks: 377.3mmol/L (42.0) versus 317.7mmol/L (39.1). The unadjusted mean difference for the population with data available at both time points (n=11) was -57.7mmol/L (95% confidence interval -85.1 to -30.3).

Table 43: Analysis of serum samples, comparison between study groups

	Baseline / Visit 1 (PN day 1-14)			Visit 4 (PN day 77-91)			
	Intervention Mean (SD)	Control Mean (SD)	Δ (I-C) [*] (95% CI)	Intervention Mean (SD)	Control Mean (SD)	Δ (I-C) [†] (95% CI)	Adj. Δ (I-C) [‡] (95% CI)
Postnatal day	11 (4)	9 (5)		90 (3)	87 (5)		
Number of observations	10	6		8	3 [§]		
Laboratory analyses ^{**}							
Urea / mmol/L	3.5 (1.1)	4.5 (1.2)	-1.0 (-2.3 to 0.3)	4.6 (1.0)	5.3 (0.5)	-0.8 (-2.2 to 0.7)	-1.3 (-3.3 to 0.8)
Creatinine / mmol/L	63.1 (10.0)	67.3 (8.7)	-4.2 (-14.8 to 6.3)	59.8 (6.9)	69.7 (6.3)	-9.9 (-20.4 to 0.5)	-2.8 (-9.8 to 4.1)
Uric acid / mmol/L	383.3 (38.3)	367.2 (49.6)	16.1 (-31.1 to 63.4)	322.3 (42.7)	305.7 (30.7)	16.6 (-45.3 to 78.4)	14.9 (-45.6 to 75.4)
Alanine aminotransferase / IU/L	18.5 (4.7)	25.3 (14.9)	-6.8 (-17.6 to 3.9)	20.6 (7.6)	19.3 (10.2)	1.3 (-11.3 to 13.9)	6.9 (-6.2 to 19.9)
Total cholesterol / mmol/L	6.6 (1.0)	7.4 (0.9)	-0.8 (-1.9 to 0.3)	5.1 (0.7)	5.6 (0.3)	-0.5 (-1.5 to 0.5)	-0.4 (-1.6 to 0.7)
Triglycerides / mmol/L	2.3 (0.8)	2.7 (2.0)	-0.4 (-1.9 to 1.2)	1.4 (0.5)	2.0 (1.3)	-0.5 (-1.7 to 0.6)	-0.7 (-1.8 to 0.4)
Glucose / mmol/L	5.4 (1.6)	4.5 (0.8)	0.9 (-0.7 to 2.4)	4.7 (0.8)	5.2 (0.3)	-0.5 (-1.6 to 0.7)	-0.6 (-1.6 to 0.3)
Insulin / pmol/L	107.6 (126.8)	49.8 (41.6)	57.8 (-58.2 to 173.7)	128.6 (194.8)	106.2 (115.0)	22.3 (-253.6 to 298.1)	-46.4 (-218.3 to 125.4)
Research analyses ^{††}							
sFlt1 / pg/ml	271.0 (173.2)	410.3 (272.8)	-139.3 (-376.5 to 97.9)	88.0 (16.2)	93.9 (18.3)	-5.9 (-36.0 to 24.1)	-3.9 (-37.8 to 30.0)
PlGF / pg/ml	13.6 (1.8)	12.9 (1.6)	0.7 (-1.1 to 2.6)	13.5 (2.6)	9.0 (1.5)	4.4 (-0.1 to 8.9)	3.4 (-1.9 to 8.8)
VEGF / pg/ml	439.2 (261.4)	258.0 (151.8)	181.2 (-71.8 to 434.1)	343.5 (153.0)	165.9 (91.5)	177.7 (-39.3 to 394.6)	99.5 (-117.8 to 316.9)
sEng / ng/ml	8.9 (4.5)	13.4 (6.4)	-4.5 (-10.3 to 1.3)	4.5 (0.8)	4.3 (0.3)	0.2 (-1.2 to 1.6)	0.1 (-1.3 to 1.5)

Abbreviations: C = control; 95% CI = 95% confidence interval; I = intervention; PlGF = placental growth factor; PN = postnatal; SD = standard deviation; sEng = soluble endoglin; sFlt-1 = soluble FMS-like tyrosine kinase 1; VEGF = vascular endothelial growth factor

^{*} Raw difference between groups presented for baseline data

[†] Raw difference between groups for follow-up data

[‡] Adjusted difference calculated using linear regression model, adjusting for baseline result

[§] In the control group for sFlt1, PlGF and sEng only two samples available for control group as inadequate sample from one patient

^{**} No haematology results available due to sample processing error

^{††} Analyses conducted using Quantikine® ELISAs (enzyme-linked immunosorbent assays), R&D Systems®, employing the quantitative sandwich enzyme immunoassay technique. Plates were read using a microplate reader set to 450nm, with wavelength correction of 570nm.

Table 44: Analysis of serum samples, comparison between time points

	Baseline / Visit 1 (PN day 1-14) Mean (SD)	Visit 4 (PN day 77-91) Mean (SD)	Δ (I-C) ^{††} (95% CI)
Number of observations	16	11 ^{§§}	10 ^{***}
sFlt1 / pg/ml	323.3 (218.3)	89.1 (15.7)	-152.2 (-267.1 to -37.3)*
PlGF / pg/ml	13.3 (1.7)	12.6 (3.0)	-0.6 (-2.4 to 1.2)
VEGF / pg/ml	371.3 (238.5)	295.1 (157.9)	-79.0 (-205.4 to 47.5)
sEng / ng/ml	10.6 (5.5)	4.5 (0.7)	-3.4 (-6.1 to -0.7)*

Abbreviations: 95% CI = 95% confidence interval; PlGF = placental growth factor; PN = postnatal; SD = standard deviation; sEng = soluble endoglin; sFlt-1 = soluble FMS-like tyrosine kinase 1; VEGF = vascular endothelial growth factor

^{††} Unadjusted mean differences calculated with paired two-sample t-tests

^{§§} At follow-up for sFlt1, PlGF and sEng only ten samples available as inadequate sample from one patient

^{***} Population with data available at both time points for comparison

6.5 Discussion

6.5.1 Main findings

The main results of this sub-study have shown that undertaking these measures in this population was feasible whilst conducting the main trial. This study was not powered to detect potential differences between groups in order to adequately address the hypothesis that improved postpartum BP control may ameliorate women's long-term cardiovascular risk through vascular and/or cardiac remodelling.

Notwithstanding this, it was reassuring that, with respect to trends across time, the majority of results were as expected. Most of the markers of arterial stiffness showed a reduction, albeit non-significant, between the two time points, consistent with the predicted partial postpartum recovery (337). The exception was the Alx, which appeared to increase postpartum, suggesting an increase in arterial stiffness during this period. This trend has been suggested when pulse wave analysis has previously been performed postpartum following both normal and hypertensive pregnancies (367). However, it should be acknowledged that obtaining reliable pulse waveforms was challenging in this group, particularly immediately postpartum, due an increased mean BMI, the increased tissue oedema seen postpartum and the presence of a young infant at the visits often limiting the time that could be spent obtaining a reliable measure. These factors may have influenced the accuracy of measures more profoundly at the baseline visit, than at three-months postpartum (especially the tissue oedema, which will have resolved by this stage), which may have affected the trend seen between the visits.

The fall noted in sFlt-1, sEng, PlGF and VEGF between baseline and 12 week follow-up was consistent with what would have been predicted, given that these markers originate from the placenta, and are elevated during pregnancy (69). The drop was non-significant for the angiogenic factors, which is likely to be a result of the sub-study's lack of power.

Both the absolute values and longitudinal temporal trends in conventional serum markers of the end-organ effects of HDP were consistent with those expected. It is known that during pregnancy the kidneys become more 'efficient' due to increased renal blood flow secondary to vasodilation, resulting in a higher filtration rate, producing lower serum urea and creatinine values than are seen outside pregnancy (368). Only 1-5% women with HDP will suffer renal impairment as part of their condition (369, 370), so it is unsurprising that the trend in this data reflected the normal population as opposed to the minority of women with acute kidney injury as part of their hypertensive disorder of pregnancy. In contrast, the uric acid fell significantly between baseline and 12 weeks, in line with previous reports that it is a more sensitive and specific marker for HDP than creatinine (371).

These data do provide evidence that the measures undertaken are feasible in this population, and some support for their consistency in this setting. A concern exists surrounding the reproducibility of the pulse wave analysis measures, and the accuracy of pulse wave analysis needs evaluating further in this population.

6.5.2 Strengths and weaknesses

In this small sub-study the control group included a higher proportion of women with pre-eclampsia than did the intervention group (67% versus 50%), but had a lower median PCR and a longer duration of antenatal antihypertensive medication, both potentially suggestive of less severe, more stable hypertensive disease. However, the mean gestational ages at diagnosis and delivery did not differ between the groups. The intervention group, on average, had both their baseline and follow-up visits occur slightly later than did the control group (11 versus nine days postpartum for the baseline visit), which particularly at baseline may have altered these results. These factors may help explain the non-significant differences noted between the groups at baseline, with the control group having higher sFlt-1 and sEng levels, and lower PlGF and VEGF levels.

From a feasibility point of view, difficulties arose in retaining participants in this sub-study, to a much greater extent than in the main trial, or the qualitative sub-study: only 30% (11/37) of those who

originally consented to participate, and were randomised, completed both visits; compared to 90% (82/91) retention in the main study. This was potentially related to the time commitment and travel involved in participation in this sub-study. The consequence of this was that the sample size in this sub-study was smaller than planned, making it impossible to produce any meaningful results as regards differences in markers of vascular risk between groups, which could have resulted from the improved BP control that was seen in the intervention group (section 4.5.3.4).

Chapter 7: Conclusions

7.1 Overview

This chapter provides an overall summary of the main conclusions from this body of work.

7.2 Epidemiology

The literature review conducted supports the oft-quoted incidence of one in ten pregnancies being affected by HDP (section 1.4): 1% chronic hypertension (26), 6% gestational hypertension (22) and 3% pre-eclampsia (21). These data, all from the developed world, are supported by estimates from low and middle-income countries: data from the PRE-EMPT initiative reported that approximately 10% of pregnancies were hypertensive (372). Local audit data (section 3.3.3) showed approximately 50 pregnancies per month (7% of total) were coded as hypertensive, and on review of the medical records, half of these women were discharged home postpartum on antihypertensive medication (3.5%). Whilst this was a small sample from a single NHS Trust, comparisons with the international figures suggest these estimates tend to the conservative. There were 697,852 live births in England and Wales in 2015 (373). Therefore, approximately 70,000 pregnancies each year are affected by hypertension in the UK, and these audit data estimate that approximately 25,000 women annually will require antihypertensive medication following postpartum discharge.

7.3 Hypertensive disorders of pregnancy postpartum

There are limited high-quality data available to define the postpartum course of hypertension (section 1.7.1), however, it is clear that hypertension does persist, often for several weeks or months (mean duration 5.4 weeks (84)), and that the rate of recovery is unpredictable (83). Data from the SNAP-HT pilot study (Chapter 4) echo this, and support the hypothesis that women spend relatively more time hypertensive postpartum than antepartum (mean antenatal duration of treatment 15.2 days versus mean postnatal duration of treatment 44.2 days). In conclusion, it is clear that, in the UK, HDP present a significant burden of disease, which continues into the postpartum period. During

this time, women and their healthcare teams are subject to multiple competing pressures, which have the capacity to adversely impact on the quality of their hypertension management.

In the developed world, substantial inroads have been made to reduce the maternal mortality, and morbidity, resulting from HDP (section 1.4). In the UK, during the last decade the mortality rate has fallen from 0.83 (2006-8) (16), to 0.11 per 100,000 maternities (2012-14) (20), and from the second to the eighth leading direct cause of maternal death. More strikingly, this represents a 90% reduction in the death rate since the first triennial maternal mortality report (1952-1954) (374).

Despite these strides forward, the majority of deaths occurred postpartum (11/14, 78% from 2009-2014), and in 13/14 (93%) of cases the review of maternal deaths found that 'improvements to care could have made a difference to the outcome' (20).

Data exist suggesting that a considerable proportion of the complications of HDP occur after birth, with half of strokes (95) and a third of seizures (90, 92) occurring postpartum. Whilst a proportion of these will occur in the immediate postnatal period when women normally remain in hospital, this is reported to not be universally the case. 14-79% of postpartum seizures occur beyond the first 48 hours (90-92), and retrospective data from the USA demonstrates a post-discharge postpartum acute cerebrovascular event rate of 14.8/100,000 (96), similar to previously published rates of all postpartum acute cerebrovascular disease (8-22 /100,000 deliveries) (97, 98). Collectively these data lend support to the thesis that the postpartum period does matter in women who have suffered hypertensive pregnancies. Severe systolic hypertension has been shown to predict stroke risk in HDP (95), and degree of hypertension has been recommended as one factor in the assessment of eclampsia risk (375). Therefore, more consistent, regular postpartum BP monitoring may help to better identify women at increased risk of serious morbidity, and it is possible that improved BP control during this time may help to mitigate this risk.

The mortality data from low and middle income countries is less optimistic, with HDP remaining the second leading cause of maternal death worldwide (376), responsible for approximately 30,000

deaths annually (377). Addressing the global burden of HDP is outside the scope of this thesis, however mHealth has been proposed as a potential solution for detection and surveillance in this context, given the rapid spread of mobile phone use worldwide (378). A low-cost, accurate, oscillometric BP monitor (379) and a smartphone app prediction model for HDP (380) have been developed. The research groups behind these initiatives propose that the utility of these interventions could be extended into the postnatal period, given the need for ongoing monitoring, and additionally the potential to identify women at risk of CVD in later life (374).

7.4 Existing evidence

The systematic review undertaken during this thesis (Chapter 2) reinforced the conclusions of the Cochrane review (89), the NICE guideline (1) and the 2014 Annual Report of the Chief Medical Officer (77), that there is a shortage of good quality evidence underpinning management strategies for postpartum hypertension. In particular, the findings of the broad and inclusive review reported in Chapter 2 highlighted no published evidence guiding the selection of BP thresholds for medication adjustment; the choice of antihypertensive for BP management following postpartum hospital discharge; or how to approach antihypertensive dose adjustment during the postnatal period. Insufficient evidence exists regarding both the organisation of postnatal care and the use of adjunctive treatments, including diuretics, parenteral steroids, SSRIs, alternative treatments and uterine curettage.

This evidence gap helps to explain the lack of substantive recommendations for postpartum management provided by all national and international guidelines (section 1.7.3) and the inconsistencies in care provision identified by the audit and survey (Chapter 3). The audit identified inadequate handover of care as an issue in half of cases, and in the survey there was significant variation in the approach to medication adjustment (section 3.4.3.4), and in the BP thresholds used to guide titration (section 3.4.3.3). The paucity of robust evidence and guidance for postpartum BP

management reinforces the need for further good-quality research into comprehensive care strategies, as recommended by the Chief Medical Officer (77).

7.5 SNAP-HT pilot randomised trial

To this end, a pilot RCT evaluating self-management of postnatal antihypertensive treatment was conducted (SNAP-HT – Chapter 4). Self-management has been shown to be effective in essential hypertension, resulting in significant BP reductions at 12 months (118, 119), so this approach was trialled in women with HDP requiring ongoing antihypertensive treatment postpartum. The course of the disorder is normally relatively short-lived, a recent pregnancy may motivate women to engage with their health, and young women are likely to be comfortable engaging with mobile health technology. Together these factors may result in greater acceptability and better results.

The recruitment (~50%), retention (90%) and compliance with follow-up rates (98%) suggest expanding the study to a larger scale should be practicable. BP outcomes from the trial were encouraging, despite the fact that the pilot study was not powered to detect a difference. Improved BP control was seen six weeks postpartum with self-management, with both a lower mean BP (adjusted difference -5.2mmHg (95% confidence interval -9.3 to -1.2)/-5.8mmHg (95% confidence interval -9.1 to -2.5)) and a greater likelihood of having a BP within the target range (adjusted OR 8.0 (95% confidence interval 2.1 to 30.6)). The difference in mean DBP persisted from four weeks through to six months (adjusted difference -4.5mmHg (95% confidence interval -8.1 to 0.8)), despite the vast majority of women from both groups having ceased all antihypertensive treatment by this stage. The consistent and persistent nature of these changes is suggestive of a true effect albeit one that needs testing in a larger trial. High median compliance (80%) and accuracy (87%) data for daily HBPM whilst on treatment underline why the intervention was effective. Safety data from this pilot study were also reassuring, with similar rates of SAEs and side effects being reported by the two groups.

7.6 By what mechanism(s) might self-management lower blood pressure?

The question arises: how did self-management result in lower BP? The data presented (Chapter 4) suggest this was not due to a longer duration of antihypertensive treatment: intervention group median duration 29 days (17-49), versus control group median duration 40.5 days (22.5-58). Nor was it related to higher doses of antihypertensive treatment: at all time points the median WHO defined daily doses in the two groups were similar (Table 28). Medication adherence was not measured during the pilot study, but this has been reported to be relevant in essential hypertension (292).

The qualitative interviews (Chapter 5) suggested participants generally expressed a preference for self-management and felt more in control of their condition as a result of the intervention. These qualitative data also revealed that participants perceived self-management as more convenient, flexible and reactive to the development of problems and the need to down-titrate medications, than usual care. Given the extent of discussion in these interviews about the role of reminders within the telemonitoring system, it may also have been that HBPM served as a prompt to take medication, during a challenging time period. Self-management, through increased monitoring and the capacity for more responsive medication adjustment, may also have better selected which women did, and did not, require antihypertensive treatment, and during the interviews women reported believing this to be the case (section 5.4.2.1).

7.7 Hypertensive disorders of pregnancy and long-term cardiovascular risk: summary

HDP are associated with a two to three-fold increase in the risk of CVD in later life (108), and it is apparent that much of this risk is related to an increased incidence of essential hypertension (110). Gestational hypertension and pre-eclampsia are both cited as major risk factors by the American Heart Association (2011) (112). Postpartum BP appears to be important in this regard, with the degree of hypertension six weeks postpartum correlating with BP several years later (87, 111).

Pathophysiological data underpin these epidemiological observations, with cardiac and vascular remodelling being shown to persist postpartum (296, 337, 342). The persistent reduction of DBP observed from four weeks to six months during this pilot study (Chapter 4) may reflect a beneficial impact of better BP control on postpartum cardiac and vascular remodelling. The sub-study reported in Chapter 6 was too small to provide substantive data to support or refute this hypothesis, but the trends observed within the whole sub-study population reflected the previously described partial cardiovascular recovery (294), suggesting possible utility of these measures if employed within a larger population.

7.8 Implications for practice

Review of the existing evidence fails to produce conclusive recommendations for management; however, the commonly utilised antihypertensive medications appear to be effective in terms of BP lowering albeit the lack of data may mask important differences. This lack of good quality evidence helps to explain the lack of explicit recommendations, worldwide, which have been published to guide postpartum management of HDP. From this research the NICE guideline appears to be most thorough (1). The pilot trial suggests that self-management may be a feasible, effective and acceptable strategy for the management of HDP postpartum. However, thus far, this has been incompletely evaluated, and therefore routine implementation cannot yet be recommended.

7.9 Recommendations for research

The postnatal period often falls into the shadow of pregnancy and childbirth, but in view of the proportion of both complications that occur after delivery and postnatal readmissions attributable to hypertension, it should not be overlooked when considering HDP management. HBPM, supported by telemonitoring, appears to be a promising management strategy in postpartum women with HDP, and large-scale evaluation is justified by both the pilot study and the paucity of existing evidence for effective alternatives.

7.10 Final conclusions

This thesis provides an overview of the current state of postpartum hypertension research, and a snapshot of some of the inconsistencies that exist in clinical practice. It demonstrates the feasibility, acceptability and potential effectiveness of self-management in this clinical scenario, and represents the first proposal of a comprehensive model of postnatal care for women with HDP. The medium-term BP data reinforce the notion that postpartum BP control may impact long-term cardiovascular risk.

References

1. National Institute for Health and Care Excellence. NICE Clinical Guideline 107: Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. 2011.
2. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. *Pregnancy Hypertens.* 2014;4(2):97-104.
3. PRECOG Development Group. PRECOG: The Pre-eclampsia Community Guideline. Action on Pre-eclampsia; 2004.
4. PRECOG Development Group. Pre-eclampsia Day Assessment Unit Guideline for midwives. 2009.
5. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;32(24):3147-97.
6. World Health Organisation. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011.
7. Lindheimer MD, Taler SJ, Cunningham FG. Hypertension in pregnancy. *J Am Soc Hypertens.* 2008;2(6):484-94.
8. ACOG Task Force on Hypertension in Pregnancy. Hypertension in Pregnancy. American College of Obstetricians and Gynecologists; 2013.
9. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P, Canadian Hypertensive Disorders of Pregnancy Working Group. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *Pregnancy Hypertens.* 2014;4(2):105-45.
10. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton M, North RA, et al. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. *Aust N Z J Obstet Gynaecol.* 2015;55(5):e1-e29.
11. Weinstein L. Syndrome of hemolysis, elevated liver enzymes, and low platelet count: a severe consequence of hypertension in pregnancy. *Am J Obstet Gynecol.* 1982;142(2):159-67.
12. Pritchard JA, Weisman R, Jr., Ratnoff OD, Vosburgh GJ. Intravascular hemolysis, thrombocytopenia and other hematologic abnormalities associated with severe toxemia of pregnancy. *N Engl J Med.* 1954;250(3):89-98.
13. McKay DG. Hematologic evidence of disseminated intravascular coagulation in eclampsia. *Obstet Gynecol Surv.* 1972;27(6):399-417.
14. Killam AP, Dillard SH, Patton RC, Pederson PR. Pregnancy-induced hypertension complicated by acute liver disease and disseminated intravascular coagulation. Five case reports. *Am J Obstet Gynecol.* 1975;123(8):823-8.

15. Tranquilli AL, Brown MA, Zeeman GG, Dekker G, Sibai BM. The definition of severe and early-onset preeclampsia. Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Pregnancy Hypertens.* 2013;3(1):44-7.
16. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *Br J Obstet Gynaecol.* 2011;118 Suppl 1:1-203.
17. American College of Obstetricians and Gynecologists. Diagnosis and management of preeclampsia and eclampsia. ACOG Practice Bulletin. ACOG Practice Bulletin No. 33; 2002.
18. Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJ. Saving Lives, Improving Mothers' Care - Lessons learned to inform future maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–12.: Oxford: National Perinatal Epidemiology Unit, University of Oxford, MMBRACE-UK; 2014.
19. Knight M, Tuffnell D, Kenyon S, Shakespeare J, Gray R, Kurinczuk JJ. Saving Lives, Improving Mothers' Care - Surveillance of maternal deaths in the UK 2011-13 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-13. Oxford: National Perinatal Epidemiology Unit, University of Oxford, MBRRACE-UK; 2015.
20. Knight M, Nair M, Tuffnell D, Kenyon S, Shakespeare J, Brocklehurst P, et al. Saving Lives, Improving Mother's Care - Surveillance of maternal deaths in the UK 2012-14 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries in Maternal Deaths and Morbidity 2009-14. Oxford: National Perinatal Epidemiology Unit, University of Oxford, MBRRACE-UK; 2016.
21. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. *BMJ.* 2013;347:f6564.
22. Yoder SR, Thornburg LL, Bisognano JD. Hypertension in pregnancy and women of childbearing age. *Am J Med.* 2009;122(10):890-5.
23. National Institute for Health and Care Excellence. NICE Clinical Guideline 107: Hypertension in pregnancy: Costing report. Implementing NICE guidance.; 2010.
24. Wallis AB, Saftlas AF, Hsia J, Atrash HK. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987-2004. *Am J Hypertens.* 2008;21(5):521-6.
25. Sibai BM, Caritis SN, Thom E, Klebanoff M, McNellis D, Rocco L, et al. Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med.* 1993;329(17):1213-8.
26. Bateman BT, Bansil P, Hernandez-Diaz S, Mhyre JM, Callaghan WM, Kuklina EV. Prevalence, trends, and outcomes of chronic hypertension: a nationwide sample of delivery admissions. *Am J Obstet Gynecol.* 2012;206(2):134.e1-8.
27. Zwart JJ, Richters A, Ory F, de Vries JIP, Bloemenkamp KWM, van Roosmalen J. Eclampsia in the Netherlands. *Obstet Gynecol.* 2008;112(4):820-7.

28. Knight M, UKOSS. Eclampsia in the United Kingdom 2005. *Br J Obstet Gynaecol*. 2007;114(9):1072-8.
29. Douglas KA, Redman CW. Eclampsia in the United Kingdom. *BMJ*. 1994;309(6966):1395-400.
30. Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: case-control study. *BMJ*. 2001;322(7294):1089-93.
31. Lindquist A, Knight M, Kurinczuk JJ. Variation in severe maternal morbidity according to socioeconomic position: a UK national case-control study. *BMJ Open*. 2013;3(6).
32. Mahendru AA, Everett TR, Wilkinson IB, Lees CC, McEniery CM. A longitudinal study of maternal cardiovascular function from preconception to the postpartum period. *J Hypertens*. 2014;32(4):849-56.
33. Ishikuro M, Obara T, Metoki H, Ohkubo T, Yamamoto M, Akutsu K, et al. Blood pressure measured in the clinic and at home during pregnancy among nulliparous and multiparous women: the BOSHI study. *Am J Hypertens*. 2013;26(1):141-8.
34. Christianson RE. Studies on blood pressure during pregnancy. I. Influence of parity and age. *Am J Obstet Gynecol*. 1976;125(4):509-13.
35. Page EW. The relation between hydatid moles, relative ischemia of the gravid uterus and the placental origin of eclampsia. *Am J Obstet Gynecol*. 1939;37:291-3.
36. Visser W, Wallenburg HC. Central hemodynamic observations in untreated preeclamptic patients. *Hypertension*. 1991;17(6 Pt 2):1072-7.
37. Karumanchi SA, Maynard SE, Stillman IE, Epstein FH, Sukhatme VP. Preeclampsia: a renal perspective. *Kidney Int*. 2005;67(6):2101-13.
38. Brennecke SP, Gude NM, Di Iulio JL, King RG. Reduction of placental nitric oxide synthase activity in pre-eclampsia. *Clin Sci (Lond)*. 1997;93(1):51-5.
39. Ward K, Hata A, Jeunemaitre X, Helin C, Nelson L, Namikawa C, et al. A molecular variant of angiotensinogen associated with preeclampsia. *Nat Genet*. 1993;4(1):59-61.
40. Roberts JM, Cooper DW. Pathogenesis and genetics of pre-eclampsia. *Lancet*. 2001;357(9249):53-6.
41. Brosens IA, Robertson WB, Dixon HG. The role of the spiral arteries in the pathogenesis of pre-eclampsia. *J Pathol*. 1970;101(4):Pvi.
42. Red-Horse K, Zhou Y, Genbacev O, Prakobphol A, Foulk R, McMaster M, et al. Trophoblast differentiation during embryo implantation and formation of the maternal-fetal interface. *J Clin Invest*. 2004;114(6):744-54.
43. Granger JP, LaMarca BB, Cockrell K, Sedeek M, Balzi C, Chandler D, et al. Reduced uterine perfusion pressure (RUPP) model for studying cardiovascular-renal dysfunction in response to placental ischemia. *Methods Mol Med*. 2006;122:383-92.
44. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. *Science*. 2005;308(5728):1592-4.

45. Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. *Am J Obstet Gynecol*. 2013;209(6):544.e1-e12.
46. Ness RB, Roberts JM. Heterogeneous causes constituting the single syndrome of preeclampsia: a hypothesis and its implications. *Am J Obstet Gynecol*. 1996;175(5):1365-70.
47. Luo ZC, An N, Xu HR, Larante A, Audibert F, Fraser WD. The effects and mechanisms of primiparity on the risk of pre-eclampsia: a systematic review. *Paediatr Perinat Epidemiol*. 2007;21(Suppl 1):36-45.
48. Hernandez-Diaz S, Toh S, Cnattingius S. Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. *BMJ*. 2009;338.
49. Tubbergen P, Lachmeijer AM, Althuisius SM, Vlak ME, van Geijn HP, Dekker GA. Change in paternity: a risk factor for preeclampsia in multiparous women? *J Reprod Immunol*. 1999;45(1):81-8.
50. Dekker GA, Robillard PY, Hulsey TC. Immune maladaptation in the etiology of preeclampsia: a review of corroborative epidemiologic studies. *Obstet Gynecol Surv*. 1998;53(6):377-82.
51. Wang JX, Knottnerus AM, Schuit G, Norman RJ, Chan A, Dekker GA. Surgically obtained sperm, and risk of gestational hypertension and pre-eclampsia. *Lancet*. 2002;359(9307):673-4.
52. Robillard PY, Hulsey TC. Association of pregnancy-induced-hypertension, pre-eclampsia, and eclampsia with duration of sexual cohabitation before conception. *Lancet*. 1996;347(9001):619.
53. Robillard PY, Hulsey TC, Perianin J, Janky E, Miri EH, Papiernik E. Association of pregnancy-induced hypertension with duration of sexual cohabitation before conception. *Lancet*. 1994;344(8928):973-5.
54. Chesley LC, Cooper DW. Genetics of hypertension in pregnancy: possible single gene control of pre-eclampsia and eclampsia in the descendants of eclamptic women. *Br J Obstet Gynaecol*. 1986;93(9):898-908.
55. Elliot GTJ. Case 120: Puerperal eclampsia in the eighth month; extraordinary family history. *Obstetrical Clinic*. New York: Appleton; 1873. p. 291-3.
56. Cincotta RB, Brennecke SP. Family history of pre-eclampsia as a predictor for pre-eclampsia in primigravidas. *Int J Gynaecol Obstet*. 1998;60(1):23-7.
57. Lachmeijer AMA, Dekker GA, Pals G, Aarnoudse JG, ten Kate LP, Arngimsson R. Searching for preeclampsia genes: the current position. *Eur J Obstet Gynecol Reprod Biol*. 2002;105(2):94-113.
58. Fisher SJ. Why is placentation abnormal in preeclampsia? *Am J Obstet Gynecol*. 2015;213(Suppl 4):S115-S22.
59. Roberts JM, Hubel CA. Is oxidative stress the link in the two-stage model of pre-eclampsia? *Lancet*. 1999;354(9181):788-9.
60. Chappell LC, Seed PT, Briley AL, Kelly FJ, Lee R, Hunt BJ, et al. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. *Lancet*. 1999;354(9181):810-6.

61. Rumbold A, Ota E, Hori H, Miyazaki C, Crowther CA. Vitamin E supplementation in pregnancy. *Cochrane Database Syst Rev*. 2015(9).
62. Rumbold A, Ota E, Nagata C, Shahrook S, Crowther CA. Vitamin C supplementation in pregnancy. *Cochrane Database Syst Rev*. 2015(9).
63. Lau SY, Guild SJ, Barrett CJ, Chen Q, McCowan L, Jordan V, et al. Tumor necrosis factor-alpha, interleukin-6, and interleukin-10 levels are altered in preeclampsia: a systematic review and meta-analysis. *Am J Reprod Immunol*. 2013;70(5):412-27.
64. Kalinderis M, Papanikolaou A, Kalinderi K, Ioannidou E, Giannoulis C, Karagiannis V, et al. Elevated serum levels of interleukin-6, interleukin-1beta and human chorionic gonadotropin in pre-eclampsia. *Am J Reprod Immunol*. 2011;66(6):468-75.
65. Kuntz TB, Christensen RD, Stegner J, Duff P, Koenig JM. Fas and Fas ligand expression in maternal blood and in umbilical cord blood in preeclampsia. *Pediatr Res*. 2001;50(6):743-9.
66. Page NM, Woods RJ, Gardiner SM, Lomthaisong K, Gladwell RT, Butlin DJ, et al. Excessive placental secretion of neurokinin B during the third trimester causes pre-eclampsia. *Nature*. 2000;405(6788):797-800.
67. Savvidou MD, Hingorani AD, Tsikas D, Frolich JC, Vallance P, Nicolaides KH. Endothelial dysfunction and raised plasma concentrations of asymmetric dimethylarginine in pregnant women who subsequently develop pre-eclampsia. *Lancet*. 2003;361(9368):1511-7.
68. Gastrich MD, Faro R, Rosen T. Markers of preeclampsia and the relationship to cardiovascular disease: review of the twenty-first century literature. *J Matern Fetal Neonatal Med*. 2010;23(8):751-69.
69. Rana S, Karumanchi SA, Lindheimer MD. Angiogenic factors in diagnosis, management, and research in preeclampsia. *Hypertension*. 2014;63(2):198-202.
70. Zygmunt M, Herr F, Munstedt K, Lang U, Liang OD. Angiogenesis and vasculogenesis in pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2003;110(Suppl 1):S10-S8.
71. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest*. 2003;111(5):649-58.
72. Levine RJ, Lam C, Qian C, Yu KF, Maynard SE, Sachs BP, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. *N Engl J Med*. 2006;355(10):992-1005.
73. Verlohren S, Galindo A, Schlembach D, Zeisler H, Herraiz I, Moertl MG, et al. An automated method for the determination of the sFlt-1/PIGF ratio in the assessment of preeclampsia. *Am J Obstet Gynecol*. 2010;202(2):161.e1-e11.
74. Verlohren S, Herraiz I, Lapaire O, Schlembach D, Zeisler H, Calda P, et al. New gestational phase-specific cutoff values for the use of the soluble fms-like tyrosine kinase-1/placental growth factor ratio as a diagnostic test for preeclampsia. *Hypertension*. 2014;63(2):346-52.
75. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med*. 2004;350(7):672-83.

76. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, et al. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. *N Engl J Med*. 2016;374(1):13-22.
77. Davies SC. Annual Report of the Chief Medical Officer, 2014 - The Health of the 51%: Women. 2015.
78. Goel A, Maski MR, Bajracharya S, Wenger JB, Zhang D, Salahuddin S, et al. Epidemiology and Mechanisms of De Novo and Persistent Hypertension in the Postpartum Period. *Circulation*. 2015;132(18):1726-33.
79. Working Group on High Blood Pressure in Pregnancy. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol*. 2000;183(1):S1-S22.
80. Walters BN, Walters T. Hypertension in the puerperium. *Lancet*. 1987;2(8554):330.
81. Stepan H, Nordmeyer AK, Faber R. Proteinuria in hypertensive pregnancy diseases is associated with a longer persistence of hypertension postpartum. *J Hum Hypertens*. 2006;20(2):125-8.
82. Ferrazzani S, De Carolis S, Pomini F, Testa AC, Mastromarino C, Caruso A. The duration of hypertension in the puerperium of preeclamptic women: relationship with renal impairment and week of delivery. *Am J Obstet Gynecol*. 1994;171(2):506-12.
83. Berks D, Steegers EA, Molas M, Visser W. Resolution of hypertension and proteinuria after preeclampsia. *Obstet Gynecol*. 2009;114(6):1307-14.
84. Podymow T, August P. Postpartum course of gestational hypertension and preeclampsia. *Hypertens Pregnancy*. 2010;29(3):294-300.
85. Berks D, Hoedjes M, Van Oppenraaij R, Visser W, Steegers E, Duvekot H. Is the Severity of Preeclampsia Related to Postpartum Normalization of Proteinuria and Hypertension? *Hypertens Pregnancy*. 2008;27(4):535.
86. Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet*. 2009;374(9694):979-88.
87. Visser VS, Hermes W, Franx A, Koopmans CM, Van Pampus MG, Mol BW, et al. High blood pressure six weeks postpartum after hypertensive pregnancy disorders at term is associated with chronic hypertension. *Pregnancy Hypertens*. 2013;3(4):242-7.
88. Samwiil L, Mercer C, Jarrett P, O'Malley S, Genetics of Pre-Eclampsia Collaborative Study Research M. Blood pressure and urinalysis are often omitted in women who have suffered pre-eclampsia at their six-week postnatal check. *Br J Obstet Gynaecol*. 2004;111(6):623-6625.
89. Magee L, von Dadelszen P. Prevention and treatment of postpartum hypertension. *Cochrane Database Syst Rev*. 2013(4).
90. Chames MC, Livingston JC, Ivester TS, Barton JR, Sibai BM. Late postpartum eclampsia: a preventable disease? *Am J Obstet Gynecol*. 2002;186(6):1174-7.

91. Kayem G, Kurinczuk JJ, Spark P, Brocklehurst P, Knight M, UKOSS. Maternal and obstetric factors associated with delayed postpartum eclampsia: a national study population. *Acta Obstet Gyn Scand.* 2011;90(9):1017-23.
92. Watson DL, Sibai BM, Shaver DC, Dacus JV, Anderson GD. Late postpartum eclampsia: an update. *South Med J.* 1983;76(12):1487-9.
93. Al-Safi Z, Imudia AN, Filetti LC, Hobson DT, Bahado-Singh RO, Awonuga AO. Delayed postpartum preeclampsia and eclampsia: demographics, clinical course, and complications. *Obstet Gynecol.* 2011;118(5):1102-7.
94. Williams KP, Galerneau F, Wilson S. Changes in cerebral perfusion pressure in puerperal women with preeclampsia. *Obstet Gynecol.* 1998;92(6):1016-9.
95. Martin JN, Jr., Thigpen BD, Moore RC, Rose CH, Cushman J, May W. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. *Obstet Gynecol.* 2005;105(2):246-54.
96. Hovsepian DA, Sriram N, Kamel H, Fink ME, Navi BB. Acute cerebrovascular disease occurring after hospital discharge for labor and delivery. *Stroke.* 2014;45(7):1947-50.
97. Kittner SJ, Stern BJ, Feaser BR, Hebel R, Nagey DA, Buchholz DW, et al. Pregnancy and the risk of stroke. *N Engl J Med.* 1996;335(11):768-74.
98. Kuklina EV, Tong X, Bansil P, George MG, Callaghan WM. Trends in Pregnancy Hospitalizations That Included a Stroke in the United States From 1994 to 2007 Reasons for Concern? *Stroke.* 2011;42(9):2564-70.
99. Clark SL, Belfort MA, Dildy GA, Englebright J, Meints L, Meyers JA, et al. Emergency department use during the postpartum period: implications for current management of the puerperium. *Am J Obstet Gynecol.* 2010;203(1):38.e1-6.
100. Belfort MA, Clark SL, Saade GR, Kleja K, Dildy GA, 3rd, Van Veen TR, et al. Hospital readmission after delivery: evidence for an increased incidence of nonurogenital infection in the immediate postpartum period. *Am J Obstet Gynecol.* 2010;202(1):35.e1-7.
101. Gillon TE, Pels A, von Dadelszen P, MacDonell K, Magee LA. Hypertensive disorders of pregnancy: a systematic review of international clinical practice guidelines. *PLoS One.* 2014;9(12):e113715.
102. Medicines and Healthcare products Regulatory Agency. Drug Safety Update: ACE inhibitors and angiotensin II receptor antagonists: recommendations on how to use for breastfeeding Cardiovascular disease and lipidology2009 [Available from: <https://www.gov.uk/drug-safety-update/ace-inhibitors-and-angiotensin-ii-receptor-antagonists-recommendations-on-how-to-use-for-breastfeeding>.
103. Webster J, Koch HF. Aspects of tolerability of centrally acting antihypertensive drugs. *J Cardiovasc Pharmacol.* 1996;27(Suppl 3):S49-S54.
104. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. *Lancet.* 2005;366(9499):1797-803.

105. Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P, et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ*. 2003;326(7394):845-9.
106. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension*. 2009;53(6):944-51.
107. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ*. 2007;335(7627):974.
108. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J*. 2008;156(5):918-30.
109. Paradisi G, Biaggi A, Savone R, Ianniello F, Tomei C, Caforio L, et al. Cardiovascular risk factors in healthy women with previous gestational hypertension. *J Clin Endocrinol Metab*. 2006;91(4):1233-8.
110. Canoy D, Cairns BJ, Balkwill A, Wright FL, Khalil A, Beral V, et al. Hypertension in pregnancy and risk of coronary heart disease and stroke: A prospective study in a large UK cohort. *Int J Cardiol*. 2016;222:1012-8.
111. Lazdam M, de la Horra A, Diesch J, Kenworthy Y, Davis E, Lewandowski AJ, et al. Unique blood pressure characteristics in mother and offspring after early onset preeclampsia. *Hypertension*. 2012;60(5):1338-45.
112. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the american heart association. *Circulation*. 2011;123(11):1243-62.
113. Zoet GA, Koster MPH, Velthuis BK, de Groot CJ, Maas AHEM, Fauser BCJM, et al. Determinants of future cardiovascular health in women with a history of preeclampsia. *Maturitas*. 2015;82(2):153-61.
114. Pickering T. Recommendations for the use of home (self) and ambulatory blood pressure monitoring. American Society of Hypertension Ad Hoc Panel. *Am J Hypertens*. 1996;9(1):1-11.
115. Brown MA, Mangos G, Davis G, Homer C. The natural history of white coat hypertension during pregnancy. *Br J Obstet Gynaecol*. 2005;112(5):601-6.
116. Brown MA. Is there a role for ambulatory blood pressure monitoring in pregnancy? *Clin Exp Pharmacol Physiol*. 2014;41(1):16-21.
117. Pickering TG, Miller NH, Ogedegbe G, Krakoff LR, Artinian NT, Goff D, et al. Call to action on use and reimbursement for home blood pressure monitoring: executive summary: a joint scientific statement from the American Heart Association, American Society Of Hypertension, and Preventive Cardiovascular Nurses Association. *Hypertension*. 2008;52(1):1-9.
118. McManus RJ, Mant J, Bray EP, Holder R, Jones MI, Greenfield S, et al. Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial. *Lancet*. 2010;376(9736):163-72.

119. McManus RJ, Mant J, Haque MS, Bray EP, Bryan S, Greenfield SM, et al. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical trial. *JAMA*. 2014;312(8):799-808.
120. Stergiou GS, Bliziotis IA. Home blood pressure monitoring in the diagnosis and treatment of hypertension: a systematic review. *Am J Hypertens*. 2011;24(2):123-34.
121. Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, et al. Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA*. 2004;291(11):1342-9.
122. Baral-Grant S, Haque MS, Nouwen A, Greenfield SM, McManus RJ. Self-Monitoring of Blood Pressure in Hypertension: A UK Primary Care Survey. *Int J Hypertens*. 2012;2012.
123. Fletcher BR, Hinton L, Bray EP, Hayen A, Hobbs FR, Mant J, et al. Self-monitoring blood pressure in patients with hypertension: an internet-based survey of UK GPs. *Br J Gen Pract*. 2016;66(652):e831-e7.
124. Little P, Barnett J, Barnsley L, Marjoram J, Fitzgerald-Barron A, Mant D. Comparison of acceptability of and preferences for different methods of measuring blood pressure in primary care. *BMJ*. 2002;325(7358):258-9.
125. Parati G, Stergiou GS, Asmar R, Bilo G, de Leeuw P, Imai Y, et al. European Society of Hypertension guidelines for blood pressure monitoring at home: a summary report of the Second International Consensus Conference on Home Blood Pressure Monitoring. *J Hypertens*. 2008;26(8):1505-26.
126. Pickering TG, Miller NH, Ogedegbe G, Krakoff LR, Artinian NT, Goff D, et al. Call to action on use and reimbursement for home blood pressure monitoring: a joint scientific statement from the American Heart Association, American Society Of Hypertension, and Preventive Cardiovascular Nurses Association. *Hypertension*. 2008;52(1):10-29.
127. National Institute for Health and Care Excellence. NICE Clinical Guideline 127: Hypertension in adults: diagnosis and management. 2011.
128. Chung Y, de Greeff A, Shennan A. Validation and compliance of a home monitoring device in pregnancy: microlife WatchBP home. *Hypertens Pregnancy*. 2009;28(3):348-59.
129. Tremonti C, Beddoe J, Brown MA. Reliability of home blood pressure monitoring devices in pregnancy. *Pregnancy Hypertens*. 8:9-14.
130. O'Brien E, Petrie J, Littler W, de Swiet M, Padfield PL, Altman DG, et al. An outline of the revised British Hypertension Society protocol for the evaluation of blood pressure measuring devices. *J Hypertens*. 1993;11(6):677-9.
131. Gupta M, Shennan AH, Halligan A, Taylor DJ, de Swiet M. Accuracy of oscillometric blood pressure monitoring in pregnancy and pre-eclampsia. *Br J Obstet Gynaecol*. 1997;104(3):350-5.
132. Nouwen E, Snijder M, van Montfrans G, Wolf H. Validation of the Omron M7 and Microlife 3BTO-A blood pressure measuring devices in preeclampsia. *Hypertens Pregnancy*. 2012;31(1):131-9.

133. Waugh J, Habiba MA, Bosio P, Boyce T, Shennan A, Halligan AW. Patient initiated home blood pressure recordings are accurate in hypertensive pregnant women. *Hypertens Pregnancy*. 2003;22(1):93-7.
134. Rayburn WF, Zuspan FP, Piehl EJ. Self-monitoring of blood pressure during pregnancy. *Am J Obstet Gynecol*. 1984;148(2):159-62.
135. Barton JR, Stanziano GJ, Sibai BM. Monitored outpatient management of mild gestational hypertension remote from term. *Am J Obstet Gynecol*. 1994;170(3):765-9.
136. Bosio P, Blackwell CN, Bowler G, Boyce T, Thurston H, Waugh JJS. Automated postnatal home blood pressure monitoring identifies significant cardiovascular disease. *J Obstet Gynaecol*. 2003;23(Suppl 1):S15.
137. Lanssens D, Vandenberg T, Smeets CJ, De Canniere H, Molenberghs G, Van Moerbeke A, et al. Remote Monitoring of Hypertension Diseases in Pregnancy: A Pilot Study. *JMIR Mhealth Uhealth*. 2017;5(3):e25.
138. Hirshberg A, Bittle MD, VanDerTuyn M, Mahraj K, Asch DA, Rosin R, et al. Rapid-Cycle Innovation Testing of Text-Based Monitoring for Management of Postpartum Hypertension. *J Clin Outcomes Manag*. 2017;24(2):77-85.
139. Magee LA, von Dadelszen P, Chan S, Gafni A, Gruslin A, Helewa M, et al. Women's views of their experiences in the CHIPS (Control of Hypertension in Pregnancy Study) Pilot Trial. *Hypertens Pregnancy*. 2007;26(4):371-87.
140. Parati G, Torlasco C, Omboni S, Pellegrini D. Smartphone Applications for Hypertension Management: a Potential Game-Changer That Needs More Control. *Curr Hypertens Rep*. 2017;19(6):48.
141. Ross-McGill H, Hewison J, Hirst J, Dowswell T, Holt A, Brunskill P, et al. Antenatal home blood pressure monitoring: a pilot randomised controlled trial. *Br J Obstet Gynaecol*. 2000;107(2):217-21.
142. Peek M, Shennan A, Halligan A, Lambert PC, Taylor DJ, De Swiet M. Hypertension in pregnancy: which method of blood pressure measurement is most predictive of outcome? *Obstet Gynecol*. 1996;88(6):1030-3.
143. Taylor RS, Freeman L, North RA. Evaluation of ambulatory and self-initiated blood pressure monitors by pregnant and postpartum women. *Hypertens Pregnancy*. 2001;20(1):25-33.
144. Bray EP, Jones MI, Banting M, Greenfield S, Hobbs FD, Little P, et al. Performance and persistence of a blood pressure self-management intervention: telemonitoring and self-management in hypertension (TASMINH2) trial. *J Hum Hypertens*. 2015;29(7):436-41.
145. Ham C, Berwick D, Dixon J. Improving quality in the English NHS - a strategy for action. The King's Fund; 2016.
146. Goodwin N, Smith J, Davies A, Perry C, Rosen R, Dixon A, et al. A report to the Department of Health and the NHS Future Form - Integrated care for patients and populations: Improving outcomes by working together. Nuffield Trust and The King's Fund; 2012.

147. Wootton R, Dimmick SL, Kvedar JC. Introduction. In: Wootton R, Dimmick SL, Kvedar JC, editors. Home telehealth: Connecting care within the community: The Royal Society of Medicine Press, Oxon; 2006. p. 1-7.
148. Department of Health. NHS Five Year Forward View. In: Health Do, editor. 2014.
149. National Information Board/UK Government. Personalised Health and Care 2020: Using data and technology to transform outcomes for patients and citizens. A framework for action.; 2014.
150. Meystre S. The current state of telemonitoring: a comment on the literature. *Telemed J E Health*. 2005;11(1):63-9.
151. Pare G, Moqadem K, Pineau G, St-Hilaire C. Clinical effects of home telemonitoring in the context of diabetes, asthma, heart failure and hypertension: a systematic review. *J Med Internet Res*. 2010;12(2):e21.
152. Omboni S, Ferrari R. The role of telemedicine in hypertension management: focus on blood pressure telemonitoring. *Curr Hypertens Rep*. 2015;17(4):535.
153. Inglis SC, Clark RA, Dierckx R, Prieto-Merino D, Cleland JG. Structured telephone support or non-invasive telemonitoring for patients with heart failure. *Cochrane Database Syst Rev*. 2015(10).
154. Honan M. Apple unveils iPhone. *Macworld*. 2007.
155. Ofcom. Adults' media use and attitudes: Report 2014. In: industries IracraftUc, editor. <http://stakeholders.ofcom.org.uk/market-data-research/other/research-publications/adults/adults-media-lit-14/>; Ofcom; 2014.
156. Ipsos Connect. Ipsos Connect Tech Tracker: Quarterly Release Q3 2015. Ipsos MORI; 2015.
157. Marsden E, Lee P. Global Mobile Consumer Survey 2016: UK Cut. Deloitte; 2016.
158. Ofcom. Adults' media use and attitudes: Report 2016 2016 [Available from: https://www.ofcom.org.uk/_data/assets/pdf_file/0026/80828/2016-adults-media-use-and-attitudes.pdf].
159. Jahns R. mHealth App Developer Economics <http://mhealththeconomics.com/2014> [Available from: <http://research2guidance.com/r2g/research2guidance-mHealth-App-Developer-Economics-2014.pdf>].
160. Patient.co.uk. Patient Survey. 2012.
161. Hirst JE, Mackillop L, Loerup L, Kevat DA, Bartlett K, Gibson O, et al. Acceptability and user satisfaction of a smartphone-based, interactive blood glucose management system in women with gestational diabetes mellitus. *J Diabetes Sci Technol*. 2015;9(1):111-5.
162. Lorig KR, Mazonson PD, Holman HR. Evidence suggesting that health education for self-management in patients with chronic arthritis has sustained health benefits while reducing health care costs. *Arthritis Rheum*. 1993;36(4):439-46.
163. Hillier K, Sarnowski L-N, Mohla C, Franklin L, Millen D, Goriwoda R. The adoption and use of digital health and care record systems: International success factors. NHS England and US Department of Health and Human Services; 2016 February 2016.

164. Imison C, Castle-Clarke S, Watson R, Edwards N. Delivering the benefits of digital health care. London: Nuffield Trust; 2016 February 2016.
165. Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D, et al. Framework for design and evaluation of complex interventions to improve health. *BMJ*. 2000;321(7262):694-6.
166. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*. 2008;337:a1655.
167. Choi JN, Moon WJ. Multiple Forms of Innovation Implementation: The Role of Innovation, Individuals, and the Implementation Context. *Organ Dyn*. 2013;42(4):290-7.
168. Nicolini D. The work to make telemedicine work: a social and articulative view. *Soc Sci Med*. 2006;62(11):2754-67.
169. Murray E, Burns J, May C, Finch T, O'Donnell C, Wallace P, et al. Why is it difficult to implement e-health initiatives? A qualitative study. *Implement Sci*. 2011;6:6.
170. Lewin S, Glenton C, Oxman AD. Use of qualitative methods alongside randomised controlled trials of complex healthcare interventions: methodological study. *BMJ*. 2009;339:b3496.
171. May C, Finch T. Implementing, embedding, and integrating practices: an outline of Normalization Process Theory. *Sociology*. 2009;43(3):535-54.
172. Murray E, Treweek S, Pope C, MacFarlane A, Ballini L, Dowrick C, et al. Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. *BMC Med*. 2010;8:63.
173. Rosenberg A. Philosophy of social science. Boulder, Colorado: Westview Press, Inc.; 1988.
174. Noblitt GW, Hare RD. Meta-ethnography: synthesizing qualitative studies. Newbury Park, California: Sage; 1988.
175. Malterud K. Qualitative research: standards, challenges, and guidelines. *Lancet*. 2001;358(9280):483-8.
176. Barbour RS. The case for combining qualitative and quantitative approaches in health services research. *J Health Serv Res Policy*. 1999;4(1):39-43.
177. Black N. Why we need qualitative research. *J Epidemiol Community Health*. 1994;48(5):425-6.
178. Steckler A, Mcleroy KR, Goodman RM, Bird ST, McCormick L. Toward Integrating Qualitative and Quantitative Methods - an Introduction. *Health Educ Quart*. 1992;19(1):1-8.
179. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol*. 2010;10:1.
180. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract*. 2004;10(2):307-12.

181. Cairns AE, Pealing L, Duffy JMN, Roberts N, Tucker KL, Leeson P, et al. Postpartum management of hypertensive disorders of pregnancy: a systematic review. *BMJ Open*. 2017;7(11):e018696.
182. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4(1).
183. McManus RJ, Wilson S, Delaney BC, Fitzmaurice DA, Hyde CJ, Tobias RS, et al. Review of the usefulness of contacting other experts when conducting a literature search for systematic reviews. *BMJ*. 1998;317:1562-3.
184. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
185. Wells GA, Shea B, O'Connell D, J. P, V. W, M. L, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm].
186. Ragab A, Goda H, Raghieb M, Barakat R, El-Samanoudy A, Badawy A. Does immediate postpartum curettage of the endometrium accelerate recovery from preeclampsia-eclampsia? A randomized controlled trial. *Arch Gynecol Obstet*. 2013;288(5):1035-8.
187. Ascarelli MH, Johnson V, McCreary H, Cushman J, May WL, Martin JN, Jr. Postpartum preeclampsia management with furosemide: a randomized clinical trial. *Obstet Gynecol*. 2005;105(1):29-33.
188. Begum MR, Quadir E, Begum A, Akhter S, Rahman K. Management of hypertensive emergencies of pregnancy by hydralazine bolus injection vs continuous drip-a comparative study. *MedGenMed*. 2002;4(4).
189. Mallapur A, Renuka B, Katageri G, Nijalingappa S. Role of postpartum curettage in recovery of severe preeclampsia and eclampsia patients-a randomised controlled trial. *Int J Gynaecol Obstet*. 2015;131(Suppl 5):E191.
190. Veena P, Perivela L, Raghavan SS. Furosemide in postpartum management of severe preeclampsia: A randomized controlled trial. *Hypertens Pregnancy*. 2017;36(1):84-9.
191. United Nations Department of Economic and Social Affairs. World economic situation and prospects 2016. New York, United States of America: United Nations; 2016.
192. Vermillion ST, Scardo JA, Newman RB, Chauhan SP. A randomized, double-blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy. *Am J Obstet Gynecol*. 1999;181(4):858-61.
193. Mabie WC, Gonzalez AR, Sibai BM, Amon E. A comparative trial of labetalol and hydralazine in the acute management of severe hypertension complicating pregnancy. *Obstet Gynecol*. 1987;70(3 Pt 1):328-33.
194. Hennessy A, Thornton CE, Makris A, Ogle RF, Henderson-Smart DJ, Gillin AG, et al. A randomised comparison of hydralazine and mini-bolus diazoxide for hypertensive emergencies in pregnancy: the PIVOT trial. *Aust N Z J Obstet Gynaecol*. 2007;47(4):279-85.

195. Garden A, Davey DA, Dommissie J. Intravenous labetalol and intravenous dihydralazine in severe hypertension in pregnancy. *Clin Exp Hypertens B*. 1982;1(2-3):371-83.
196. Gaisin IR, Iskchakova AS, Shilina LV. Indapamide in the management of post-partum hypertension: A randomized, case-control study. *Eur Heart J*. 2013;34(Suppl 1):271.
197. York R, Brown LP, Samuels P, Finkler SA, Jacobsen B, Persely CA, et al. A randomized trial of early discharge and nurse specialist transitional follow-up care of high-risk childbearing women. *Nurs Res*. 1997;46(5):254-61.
198. Sharma KJ, Greene N, Kilpatrick SJ. Oral labetalol compared to oral extended release nifedipine for persistent postpartum hypertension: A randomized controlled trial. *Am J Obstet Gynecol*. 2016;214(Suppl 1):S27-S8.
199. Sharma KJ, Greene N, Kilpatrick SJ. Oral labetalol compared to oral nifedipine for postpartum hypertension: A randomized controlled trial. *Hypertens Pregnancy*. 2017;36(1):44-7.
200. Noronha Neto C, Maia SSB, Katz L, Coutinho IC, Souza AR, Amorim MM. Clonidine versus Captopril for Severe Postpartum Hypertension: A Randomized Controlled Trial. *PLoS One*. 2017;12(1).
201. Amorim MMR, Noronha Neto C, Maia SB, Souza ASR, Katz L, Neto AHF. Clonidine compared with captopril for severe postpartum hypertension. *Obstet Gynecol*. 2015;125(5 Suppl 1):42S.
202. Katz L, Noronha Neto C, Maia S, Coutinho I, Souza Sr A, Amorim M. Clonidine versus captopril for severe postpartum hypertension: A randomized controlled trial. *Pregnancy Hypertens*. 2015;5(Suppl 1):29-30.
203. Barton JR, Hiett AK, Conover WB. The use of nifedipine during the postpartum period in patients with severe preeclampsia. *Am J Obstet Gynecol*. 1990;162(3):788-92.
204. Sayin NC, Altundag G, Varol FG. Efficacy of alpha-methyldopa and nifedipine in the treatment of postpartum hypertension. [Turkish] Postpartum hipertansiyon tedavisinde alfametildopa ve nifedipinin etkinligi. *J Turk Ger Gynecol Assoc*. 2005;6(2):118-22.
205. Palot M, Jakob L, Decaux J. Arterial hypertensions of labor and the post-partum period. [French] Les Hypertensions Arteriellles Du Travail Et Du Post-Partum. *Rev Fr Gynecol Obstet*. 1979;74(3):173-6.
206. Griffis KR, Jr., Martin JN, Jr., Palmer SM, Martin RW, Morrison JC. Utilization of hydralazine or alpha-methyldopa for the management of early puerperal hypertension. *Am J Perinatol*. 1989;6(4):437-41.
207. Martin JN, Griffis KR, Martin RW, Hess LW, Morrison JC. Early puerperal hypertension management: hydralazine vs methyldopa. *Clin Exp Hypertens B*. 1988;8(2):431.
208. Walss Rodriguez RJ, Villarreal Ordaz F. Management of severe pre-eclampsia in the puerperium. Comparative study of sublingual nifedipine and hydralazine. *Ginecol Obstet Mex*. 1991;59:207-10.
209. Vigil-De Gracia P, Ruiz E, Lopez JC, de Jaramillo IA, Vega-Maleck JC, Pinzon J. Management of severe hypertension in the postpartum period with intravenous hydralazine or labetalol: a randomized clinical trial. *Hypertens Pregnancy*. 2007;26(2):163-71.

210. Fidler J, Smith V, De Swiet M. A randomized study comparing timolol and methyldopa in hospital treatment of puerperal hypertension. *Br J Obstet Gynaecol.* 1982;89(12):1031-4.
211. Shumard K, Yoon J, Huang C, Nitsche JF. Peripartum anti-hypertensive choice affects time to blood pressure control in treating hypertensive disorders of pregnancy. *Am J Obstet Gynecol.* 2016;214(1 Suppl):S378.
212. Ilshat Gaisin IR, Iskhakova AS, Shilina LV. Control of cardiovascular risk factors with ursodeoxycholic acid and indapamide in postpreeclamptic nursing mothers: Results from a randomized, case-control 1-year study. *Eur J Prev Cardiol.* 2014;21(Suppl 1):S120.
213. Krebs A. Tests of reserpine and phenobarbital in therapy of toxicosis of pregnancy and puerperium. *Geburtshilfe Frauenheilkd.* 1956;16(5):410-22.
214. Krebs A. Experience with serpasil and luminal in the management of pregnancy-and puerperal toxemias. *Gynaecologia.* 1956;141(4):255-60.
215. Matthews G, Gornall R, Saunders NJ. A randomised placebo controlled trial of loop diuretics in moderate/severe pre-eclampsia, following delivery. *J Obstet Gynaecol.* 1997;17(1):30-2.
216. Amorim M, Katz L, Cursino T, Coutinho I. Postpartum furosemide for accelerating recovery in women with severe preeclampsia: A randomized clinical trial. *Int J Gynaecol Obstet.* 2015;131(Suppl 5):E195.
217. Weiner CP, Socol ML. Serotonin (5HT) receptor blockade in puerperal pre-eclampsia. *Clin Exp Hypertens B.* 1982;1(2-3):195.
218. Weiner CP, Socol ML, Vaisrub N. Control of preeclamptic hypertension by ketanserin, a new serotonin receptor antagonist. *Am J Obstet Gynecol.* 1984;149(5):496-500.
219. Montenegro R, Knuppel RA, Shah D, O'Brien WF. The effect of serotonergic blockade in postpartum preeclamptic patients. *Am J Obstet Gynecol.* 1985;153(2):130-4.
220. Hladunewich MA, Derby GC, Lafayette RA, Blouch KL, Druzin ML, Myers BD. Effect of L-arginine therapy on the glomerular injury of preeclampsia: a randomized controlled trial. *Obstet Gynecol.* 2006;107(4):886-95.
221. Liu Z, Wang X, Yan N. Treatment of albuminuria in gestational hypertension puerpera in the severe preeclampsia stage by TCM therapy for stasis-removing and diuresis. *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 2009;29(3):222-4.
222. Barrilleaux PS, Martin JN, Jr., Klauser CK, Bufkin L, May WL. Postpartum intravenous dexamethasone for severely preeclamptic patients without hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome: a randomized trial. *Obstet Gynecol.* 2005;105(4):843-8.
223. Barrilleaux PS, Martin Jr J, Klauser C, Bufkin L, May W. Adjunctive intravenous dexamethasone in patients with severe preeclampsia not complicated by HELLP syndrome. *Am J Obstet Gynecol.* 2003;189(6 Suppl):S94.
224. Shigemitsu A, Akasaka J, Shigetomi H, Tsunemi T, Koike N, Iwai K, et al. Use of carperitide for postpartum diuresis of severe preeclampsia. *Pregnancy Hypertens.* 2015;5(1):145.

225. Salvatore CA, Carduz E, Ciccivizzo E, Turatti S, Gorga P. Postpartum curettage in severe toxemia with and without premature loosening of the placenta. *Matern Infanc (Sao Paulo)*. 1967;26(3):275-86.
226. Magann EF, Martin JN, Jr., Isaacs JD, Perry KG, Jr., Martin RW, Meydrech EF. Immediate postpartum curettage: accelerated recovery from severe preeclampsia. *Obstet Gynecol*. 1993;81(4):502-6.
227. Magann EF, Bass JD, Chauhan SP, Perry KG, Jr., Morrison JC, Martin JN, Jr. Accelerated recovery from severe preeclampsia: uterine curettage versus nifedipine. *J Soc Gynecol Investig*. 1994;1(3):210-4.
228. Gocmen A, Yayla M, Ceylan Erden A, Demir M, Dakdeniz N. The effect of postpartum curettage in severe preeclampsia and eclampsia in recovery (Ağır preeklampsı ve eklampsı in iyileşmesinde postpartum kuretajın etkisi). *Perinatoloji Dergisi*. 1996;4(1):24.
229. Gomez LM, De la Vega GA, Ludmir J, Padilla L, Angulo D. Immediate postpartum curettage accelerates clinical recovery in severe preeclampsia. *Obstet Gynecol*. 2005;105(4 Suppl 4):111S.
230. Alkan A, Tugrul S, Oral O, Uslu H, Kose D, Catakli FT. Effects of postpartum uterine curettage on maternal well-being in severe preeclamptic patients. *Clin Obstet Gynecol*. 2006;33(1):55-8.
231. Bibbo C, Celi A, Thomas AM, Blake-Lamb TL, Wilkins-Haug L. Does the addition of a specialized postpartum clinic improve the care of women with preeclampsia? *Obstet Gynecol*. 2014;123(5 Suppl 1):39S.
232. Berks D, Hoedjes M, Raat H, Duvekot HJ, Steegers EAP. Effects of lifestyle intervention after complicated pregnancy: Results of the Pro-Active study. *Pregnancy Hypertens*. 2015;5 (1):36-7.
233. Gerard J, Blazquez G, Lardoux H. Puerperal hypertension treated by beta-blockers; atenolol or labetalol. [French] Traitement De L'hypertension Arterielle Gravidique Par Les Betabloquants. Evaluation Comparative De L'atenolol Et Du Labetalol. *Therapie*. 1983;38(6):704-6.
234. Scardo JA, Vermillion ST, Newman RB, Chauhan SP, Hogg BB. A randomized, double-blind, hemodynamic evaluation of nifedipine and labetalol in preeclamptic hypertensive emergencies. *Am J Obstet Gynecol*. 1999;181(4):862-6.
235. Wacker JR, Wagner BK, Briesse V, Schauf B, Heilmann L, Bartz C, et al. Antihypertensive therapy in patients with pre-eclampsia: A prospective randomised multicentre study comparing dihydralazine with urapidil. *Eur J Obstet Gynecol Reprod Biol*. 2006;127(2):160-5.
236. Chandrasekaran S, Traylor J, Limaye M, Srinivas S, Durnwald C. Text messaging improves postpartum follow up in hypertensive patients. *Am J Obstet Gynecol*. 2015;212(S1):S276-S7.
237. Ehrenberg H, Mercer B. Abbreviated post-partum magnesium sulfate therapy for women with mild preeclampsia. *Am J Obstet Gynecol*. 2004;191(6):S73.
238. Ehrenberg HM, Mercer BM. Abbreviated postpartum magnesium sulfate therapy for women with mild preeclampsia: a randomized controlled trial. *Obstet Gynecol*. 2006;108(4):833-8.
239. Ossada V, Jank A, Stepan H. The impact of uterine curettage postpartum on maternal sFlt-1 concentration. *J Perinat Med*. 2016;44(3):351-4.

240. Wasden SW, Ragsdale ES, Chasen ST, Skupski DW. Do non-steroidal anti-inflammatory drugs exacerbate postpartum hypertension in patients affected with severe hypertensive disorders of pregnancy? *Reprod Sci.* 2012;1):234A.
241. Younger-Lewis D, McDonnell LA, Westcott C, Elias N, Perron S, Martin N, et al. Effect of an Intervention to Improve the Cardiovascular Health of Postpartum Women With a History of Hypertensive Disorders of Pregnancy. *Can J Cardiol.* 2016;32(4):S9.
242. Al-Waili NS, Salom KHY. Sublingual and oral nifedipine for treatment of postpartum hypertension. *Faseb J.* 2004;18(4):A600-A1.
243. Alicino R. The therapy of arterial hypertension of pregnancy toxemia by means of postpartum uterine curettage. *Riv Ostet Ginecol Prat.* 1962;44:876-81.
244. Barton JR, Prevost RR, Wilson DA, Whybrew WD, Sibai BM. Nifedipine pharmacokinetics and pharmacodynamics during the immediate postpartum period in patients with preeclampsia. *Am J Obstet Gynecol.* 1991;165(4 Pt 1):951-4.
245. Belfort MA, Moore PJ. Verapamil in the treatment of severe postpartum hypertension. *S Afr Med J.* 1988;Suid-Afrikaanse Tydskrif Vir Geneeskunde. 74(6):265-7.
246. Belfort MA, Kirshon B. Nisoldipine--a new orally administered calcium antagonist used in the treatment of severe postpartum pregnancy-induced hypertension. Preliminary results. *S Afr Med J.* 1992;Suid-Afrikaanse Tydskrif Vir Geneeskunde. 81(5):267-70.
247. Bittle MD, Scalise L, Green D, Srinivas S, Hirshberg A, Chandrasekaran S. The High-Risk Postpartum Transitional Program: A Multidisciplinary Approach to Caring for Postpartum Woman With Hypertensive Disease. *J Obstet Gynecol Neonatal Nurs.* 2014;43(Supp 1):S16.
248. Correa P, Bah MD, Berthe MA, Diab AE. Hypertension during gravido-puerperium in African women. [French] *L'hypertension Arterielle Au Cours De La Gravido-Puerperalite Chez L'africaine.* Dakar Med. 1982;27(1):154-67.
249. Dulitzky M, Rosenthal T, Barkai G, Mani A, Rabau E, Mashiach S. Nifedipine in the treatment of hypertension in pregnancy and puerperium. *Clin Exp Hypertens B.* 1987;6(1):235.
250. Hirshberg A, Srinivas S. Text message based remote monitoring in the management of postpartum hypertension. *Obstet Gynecol.* 2016;127:131S.
251. Hunter CA, Jr., Howard WF, McCormick CO, Jr. Amelioration of the hypertension of toxemia by postpartum curettage. *Am J Obstet Gynecol.* 1961;81(5):884-9.
252. Onishi S, Nakano K, Iwai K, Yamada Y, Akasaka J, Shigemitsu A, et al. Postpartum follow-up of hypertensive pregnancy using at-home web-linked mobile sphygmomanometer. *Pregnancy Hypertens.* 2015;5(1):85.
253. Robinson HA, Fort WD, Schelin EC. Postpartum curettement for hypertension. *Am J Obstet Gynecol.* 1964;88(6):788-90.
254. Rodriguez GC, Albarran HA, Zeron HM. Hemodynamic evaluation and anti-hypertensive schemes used in puerperal women following pre-eclampsia. *Mymensingh Med J.* 2012;21(2):327-32.

255. Saghir S, Rajasri A. 'Tele-health service' for home blood pressure and symptom monitoring in the management of postnatal pre-eclampsia in a district general hospital with remote geography- a pilot study. *Br J Obstet Gynaecol*. 2015;122:24.
256. Smith GN, Cusimano M, Pudwell J, Roddy M, Cho J. The maternal health clinic: An initiative for cardiovascular risk identification in women with pregnancy-related complications. *Reprod Sci*. 2014;21(3 Suppl):379A.
257. Sukerman Voldman E, Rigano F, Rodriguez S, Bin LA. Sublingual nifedipine for acute treatment of hypertension in the 3rd trimester of pregnancy and in the puerperium. [Spanish] Nifedipina Sublingual Para El Tratamiento Agudo De La Hipertension Arterial En El Iii Trimestre De La Gestacion Y En El Puerperio. *Rev Obstet Ginecol Venez*. 1985;45(1):24-7.
258. Taslimi MM, Harbin AR, Gonzalez-Ruiz A. Captopril in severe preeclampsia. *J Natl Med Assoc*. 1991;83(8):721-3.
259. Tkacheva ON, Vertkin AL, Barabashkina AV, Vasil'eva AV, Razguliaeva NF. Nebivolol effects on the cardiovascular system and the kidneys in pregnant and puerperal women with hypertension. *Ter Arkh*. 2006;78(10):56-61.
260. Wacker J, Muller J, Grischke EM, Unkels R, Bastert G. Anti-hypertensive therapy in pregnancy-induced hypertension with urapidil. *Zentralbl Gynakol*. 1994;116(5):271-3.
261. Walters BN, Redman CW. Treatment of severe pregnancy-associated hypertension with the calcium antagonist nifedipine. *Br J Obstet Gynaecol*. 1984;91(4):330-6.
262. Postpartum nifedipine for severe preeclampsia. *Emerg Med (N Y)*. 1990;22(16):34.
263. Cursino T, Katz L, Coutinho I, Amorim M. Diuretics vs. placebo for postpartum blood pressure control in preeclampsia (DIUPRE): a randomized clinical trial. *Reprod Health*. 2015;12:66.
264. Gallegos R, Sanguinetti R. [Treatment of the residual gestosis of the puerperium by curettage evacuation of the decidua]. *Prensa Med Argent*. 1961;48(37):2596-9.
265. Caughey AB. Editorial Comment: Does Immediate Postpartum Curettage of the Endometrium Accelerate Recovery From Preeclampsia–Eclampsia? A Randomized Controlled Trial. *Obstet Gynecol Surv*. 2014;69(3):121-2.
266. Joint Formulary Committee. *British National Formulary (BNF)*. 71 ed: BMJ Publishing Group Ltd and Royal Pharmaceutical Society; 2016.
267. Tan LK, de Swiet M. The management of postpartum hypertension. *Br J Obstet Gynaecol*. 2002;109(7):733-6.
268. Duley L, Gulmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. *Cochrane Database Syst Rev*. 2010(11).
269. Scherer RW, Langenberg P, von Elm E. Full publication of results initially presented in abstracts. *Cochrane Database Syst Rev*. 2007(2).
270. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev*. 2014(2).

271. Khan K. The CROWN Initiative: journal editors invite researchers to develop core outcomes in women's health. *Br J Obstet Gynaecol*. 2014;121(10):1181-2.
272. Cairns AE, Tucker KL, Leeson P, Mackillop L, McManus RJ. Survey of healthcare professionals regarding adjustment of antihypertensive medication(s) in the postnatal period in women with hypertensive disorders of pregnancy. *Pregnancy Hypertens*. 2016;6(4):256-8.
273. Bramham K, Nelson-Piercy C, Brown MJ, Chappell LC. Postpartum management of hypertension. *BMJ*. 2013;346:f894.
274. Elhassan EM, Mirghani OA, Habour AB, Adam I. Methyldopa versus no drug treatment in the management of mild pre-eclampsia. *East Afr Med J*. 2002;79(4):172-5.
275. Magee LA, von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, et al. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med*. 2015;372(5):407-17.
276. Magee LA, von Dadelszen P, Singer J, Lee T, Rey E, Ross S, et al. The CHIPS Randomized Controlled Trial (Control of Hypertension in Pregnancy Study): Is Severe Hypertension Just an Elevated Blood Pressure? *Hypertension*. 2016;68(5):1153-9.
277. Hall W, Keane P, Wang S, Debell F, Allana A, Karia P. Intensive care discharges: improving the quality of clinical handover through changes to discharge documentation. *BMJ Qual Improv Rep*. 2015;4(1).
278. van Sluisveld N, Hesselink G, van der Hoeven JG, Westert G, Wollersheim H, Zegers M. Improving clinical handover between intensive care unit and general ward professionals at intensive care unit discharge. *Intensive Care Med*. 2015;41(4):589-604.
279. Jones MI, Greenfield SM, Bray EP, Baral-Grant S, Hobbs FD, Holder R, et al. Patients' experiences of self-monitoring blood pressure and self-titration of medication: the TASMING2 trial qualitative study. *Br J Gen Pract*. 2012;62(595):e135-e42.
280. Hodgkinson JA, Tucker KL, Crawford C, Greenfield SM, Heneghan C, Hinton L, et al. Is self monitoring of blood pressure in pregnancy safe and effective? *BMJ*. 2014;349:g6616.
281. Tremonti C, Beddoe J, Brown MA. Reliability of home blood pressure monitoring devices in pregnancy. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health*. 2017;8:9-14.
282. Franssen M, Farmer A, Grant S, Greenfield S, Heneghan C, Hobbs R, et al. Telemonitoring and/or self-monitoring of blood pressure in hypertension (TASMINH4): protocol for a randomised controlled trial. *BMC Cardiovasc Disord*. 2017;17(1):58.
283. Miller R. Preparation of participant information sheets and informed consent forms 2014 [Available from: https://www.admin.ox.ac.uk/media/global/wwwadminoxacuk/localsites/researchsupport/documents/ctr/downloads/newsops/University_Core_SOP_007_v1.0_Preparation_of_Participant_Information_Sheets_and_Informed_Consent_forms.pdf].
284. Health Research Authority. [Available from: <http://www.hra-decisiontools.org.uk/consent/>].
285. Damocles Study Group NHSHTAP. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet*. 2005;365(9460):711-22.

286. Department of Health. Research Governance Framework for Health and Social Care. In: Davies SC, editor. 2nd ed 2005.
287. World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-4.
288. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ*. 2016;355:i5239.
289. General Medical Council. 0-18 years: guidance for all doctors. 2007.
290. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res*. 2013;22(7):1717-27.
291. Teare MD, Dimairo M, Shephard N, Hayman A, Whitehead A, Walters SJ. Sample size requirements to estimate key design parameters from external pilot randomised controlled trials: a simulation study. *Trials*. 2014;15:264.
292. Fletcher BR, Hartmann-Boyce J, Hinton L, McManus RJ. The Effect of Self-Monitoring of Blood Pressure on Medication Adherence and Lifestyle Factors: A Systematic Review and Meta-Analysis. *Am J Hypertens*. 2015;28(10):1209-21.
293. Sedgwick P, Greenwood N. Understanding the Hawthorne effect. *BMJ*. 2015;351:h4672.
294. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. *Hypertension*. 2011;58(4):709-15.
295. Lazdam M, de la Horra A, Diesch J, Francis J, Kenworthy Y, Shore A, et al. Unique features of long-term cardiovascular phenotype in young women with early-onset pre-eclampsia. *Pregnancy Hypertens*. 2012;2(3):259-60.
296. Estensen M-E, Remme EW, Grindheim G, Smiseth OA, Segers P, Henriksen T, et al. Increased arterial stiffness in pre-eclamptic pregnancy at term and early and late postpartum: a combined echocardiographic and tonometric study. *Am J Hypertens*. 2013;26(4):549-56.
297. Wood S, Martin U, Gill P, Greenfield SM, Haque MS, Mant J, et al. Blood pressure in different ethnic groups (BP-Eth): a mixed methods study. *BMJ Open*. 2012;2(6).
298. Wood S, Greenfield SM, Haque MS, Martin U, Gill PS, Mant J, et al. Influence of ethnicity on acceptability of method of blood pressure monitoring: a cross-sectional study in primary care. *Br J Gen Pract*. 2016;66(649):e577-e86.
299. Britten N. Qualitative interviews in medical research. *BMJ*. 1995;311(6999):251-3.
300. Chapman AL, Hadfield M, Chapman CJ. Qualitative research in healthcare: an introduction to grounded theory using thematic analysis. *J R Coll Physicians Edinb*. 2015;45(3):201-5.
301. Glaser BG, Strauss AL. The discovery of grounded theory: strategies for qualitative research. Chicago: Aldine de Gruyter; 1967.
302. Ritchie J, Lewis J. Qualitative Research Practice. London: Sage; 2003.

303. Patton MQ. How to use qualitative methods in evaluation. London: Sage; 1987. p. 108-43.
304. Field PA, Morse JM. Nursing research: the application of qualitative approaches. London: Chapman and Hall; 1989.
305. Bloor M, Wood F. Audio-recording. Keywords in Qualitative Methods. London, England: Sage; 2006. p. 17-9.
306. Coyne IT. Sampling in qualitative research. Purposeful and theoretical sampling; merging or clear boundaries? J Adv Nurs. 1997;26(3):623-30.
307. Morse JM. Strategies for sampling. In: Morse JM, editor. Qualitative Nursing Research: A Contemporary Dialogue. Newbury Park, California: Sage; 1991. p. 127-45.
308. Green J, Thorogood N. Qualitative methods for health research. London: Sage; 2004.
309. O'Reilly M, Parker N. 'Unsatisfactory Saturation': a critical exploration of the notion of saturated sample sizes in qualitative research. Qual Res. 2013;13(2):190-7.
310. Bowen GA. Naturalistic inquiry and the saturation concept: a research note. Qual Res. 2008;8(1):137-52.
311. Guest G, Bunce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. Field Methods. 2006;18(1):59-82.
312. Ziebland S, McPherson A. Making sense of qualitative data analysis: an introduction with illustrations from DIPEx (personal experiences of health and illness). Med Educ. 2006;40(5):405-14.
313. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman A, Burgess RG, editors. Analyzing Qualitative Data. London: Routledge; 1994.
314. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol. 2013;13:117.
315. Hibbard JH, Stockard J, Mahoney ER, Tusler M. Development of the Patient Activation Measure (PAM): conceptualizing and measuring activation in patients and consumers. Health Serv Res. 2004;39(4 Pt 1):1005-26.
316. W Battersby M, Ask A, M Reece M, J Markwick M, P Collins J. The Partners in Health scale: The development and psychometric properties of a generic assessment scale for chronic condition self-management. Aust J Prim Health. 2003;9(3):41-52.
317. Banner DJ, Albarran JW. Computer-assisted qualitative data analysis software: a review. Can J Cardiovasc Nurs. 2009;19(3):24-31.
318. Logan AG, Dunai A, McIsaac WJ, Irvine MJ, Tisler A. Attitudes of primary care physicians and their patients about home blood pressure monitoring in Ontario. J Hypertens. 2008;26(3):446-52.
319. Jackson CJ, Bosio P, Habiba M, Waugh J, Kamal P, Dixon-Woods M. Referral and attendance at a specialist antenatal clinic: qualitative study of women's views. Br J Obstet Gynaecol. 2006;113(8):909-13.

320. Henderson J, Redshaw M. Change over time in women's views and experiences of maternity care in England, 1995-2014: A comparison using survey data. *Midwifery*. 2017;44:35-40.
321. Ru TZ, Associate A, Hegney DG. A qualitative systematic review on the experiences of self-management in community-dwelling older women living with chronic illnesses. *JBIM Libr Syst Rev*. 2011;9(62):2778-828.
322. Frost J, Garside R, Cooper C, Britten N. A qualitative synthesis of diabetes self-management strategies for long term medical outcomes and quality of life in the UK. *BMC Health Serv Res*. 2014;14(1):348.
323. Sohanpal R, Steed L, Mars T, Taylor SJ. Understanding patient participation behaviour in studies of COPD support programmes such as pulmonary rehabilitation and self-management: a qualitative synthesis with application of theory. *NPJ Prim Care Respir Med*. 2015;25:15054.
324. Williams V, Price J, Hardinge M, Tarassenko L, Farmer A. Using a mobile health application to support self-management in COPD: a qualitative study. *Br J Gen Pract*. 2014;64(624):e392-e400.
325. Bokhour BG, Cohn ES, Cortes DE, Solomon JL, Fix GM, Elwy AR, et al. The role of patients' explanatory models and daily-lived experience in hypertension self-management. *J Gen Intern Med*. 2012;27(12):1626-34.
326. Fort MP, Alvarado-Molina N, Pena L, Mendoza Montano C, Murrillo S, Martinez H. Barriers and facilitating factors for disease self-management: a qualitative analysis of perceptions of patients receiving care for type 2 diabetes and/or hypertension in San Jose, Costa Rica and Tuxtla Gutierrez, Mexico. *BMC Fam Pract*. 2013;14:131.
327. Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. *Lancet*. 2001;357(9273):2002-6.
328. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ*. 2001;323(7323):1213-7.
329. Barrett HL, Callaway LK. Hypertensive disorders of pregnancy. *BMJ*. 2017;358:j3245.
330. Hermes W, Koopmans CM, van Pampus MG, Franx A, Bloemenkamp KWM, van der Post J, et al. Induction of labour or expectant monitoring in hypertensive pregnancy disorders at term: do women's postpartum cardiovascular risk factors differ between the two strategies? *Eur J Obstet Gynecol Reprod Biol*. 2013;171(1):30-4.
331. Lazdam M, Davis EF, Lewandowski AJ, Worton SA, Kenworthy Y, Kelly B, et al. Prevention of vascular dysfunction after preeclampsia: a potential long-term outcome measure and an emerging goal for treatment. *J Pregnancy*. 2012;2012.
332. Redman CW, Sargent IL. Placental stress and pre-eclampsia: a revised view. *Placenta*. 2009;30 Suppl A:S38-S42.
333. Luscher TF. The endothelium and cardiovascular disease--a complex relation. *N Engl J Med*. 1994;330(15):1081-3.
334. Chambers JC, Fusi L, Malik IS, Haskard DO, De Swiet M, Kooner JS. Association of maternal endothelial dysfunction with preeclampsia. *JAMA*. 2001;285(12):1607-12.

335. Hibbard JU, Korcarz CE, Nendaz GG, Lindheimer MD, Lang RM, Shroff SG. The arterial system in pre-eclampsia and chronic hypertension with superimposed pre-eclampsia. *Br J Obstet Gynaecol*. 2005;112(7):897-903.
336. Elvan-Taspinar A, Franx A, Bots ML, Bruinse HW, Koomans HA. Central hemodynamics of hypertensive disorders in pregnancy. *Am J Hypertens*. 2004;17(10):941-6.
337. Evans CS, Gooch L, Flotta D, Lykins D, Powers RW, Landsittel D, et al. Cardiovascular system during the postpartum state in women with a history of preeclampsia. *Hypertension*. 2011;58(1):57-62.
338. Melchiorre K, Sutherland GR, Baltabaeva A, Liberati M, Thilaganathan B. Maternal Cardiac Dysfunction and Remodeling in Women With Preeclampsia at Term. *Hypertension*. 2011;57(1):85-93.
339. Hibbard JU, Shroff SG, Lang RM. Cardiovascular changes in preeclampsia. *Semin Nephrol*. 2004;24(6):580-7.
340. Borghi C, Esposti DD, Immordino V, Cassani A, Boschi S, Bovicelli L, et al. Relationship of systemic hemodynamics, left ventricular structure and function, and plasma natriuretic peptide concentrations during pregnancy complicated by preeclampsia. *Am J Obstet Gynecol*. 2000;183(1):140-7.
341. Lang RM, Pridjian G, Feldman T, Neumann A, Lindheimer M, Borow KM. Left-Ventricular Mechanics in Preeclampsia. *Am Heart J*. 1991;121(6):1768-75.
342. Strobl I, Windbichler G, Strasak A, Weiskopf-Schwendinger V, Schweigmann U, Ramoni A, et al. Left ventricular function many years after recovery from pre-eclampsia. *Br J Obstet Gynaecol*. 2011;118(1):76-83.
343. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. *Hypertension*. 2008;52(5):873-80.
344. Scantlebury DC, Kane GC, Wiste HJ, Bailey KR, Turner ST, Arnett DK, et al. Left ventricular hypertrophy after hypertensive pregnancy disorders. *Heart*. 2015;101(19):1584-90.
345. Degli Esposti D, Montaguti E, Ghi T, Baronio C, Rosticci M, Cicero AFG, et al. Postpartum left ventricular systolic and diastolic function in women with severe preeclampsia. *High Blood Press Cardiovasc Prev*. 2014;21(4):318-9.
346. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension*. 2001;37(5):1236-41.
347. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55(13):1318-27.
348. Urbina EM, Williams RV, Alpert BS, Collins RT, Daniels SR, Hayman L, et al. Noninvasive assessment of subclinical atherosclerosis in children and adolescents: recommendations for standard assessment for clinical research: a scientific statement from the American Heart Association. *Hypertension*. 2009;54(5):919-50.

349. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27(21):2588-605.
350. Lewandowski AJ, Pitcher A, Banerjee R, Leeson P. Arterial stiffness: using simple surrogate measures to make sense of a biologically complex phenomenon. *Hypertens Res*. 2012;35(2):155-6.
351. Clarenbach CF, Stoewhas AC, van Gestel AJ, Latshang TD, Lo Cascio CM, Bloch KE, et al. Comparison of photoplethysmographic and arterial tonometry-derived indices of arterial stiffness. *Hypertens Res*. 2012;35(2):228-33.
352. Shirai K, Utino J, Otsuka K, Takata M. A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). *J Atheroscler Thromb*. 2006;13(2):101-7.
353. Yambe T, Yoshizawa M, Saijo Y, Yamaguchi T, Shibata M, Konno S, et al. Brachio-ankle pulse wave velocity and cardio-ankle vascular index (CAVI). *Biomed Pharmacother*. 2004;58(Suppl 1):S95-S8.
354. Kim B, Takada K, Oka S, Misaki T. Influence of blood pressure on cardio-ankle vascular index (CAVI) examined based on percentage change during general anesthesia. *Hypertens Res*. 2011;34(6):779-83.
355. Sun CK. Cardio-ankle vascular index (CAVI) as an indicator of arterial stiffness. *Integr Blood Press Control*. 2013;6:27-38.
356. Shirai K, Song M, Suzuki J, Kurosu T, Oyama T, Nagayama D, et al. Contradictory effects of beta1- and alpha1- adrenergic receptor blockers on cardio-ankle vascular stiffness index (CAVI)--CAVI independent of blood pressure. *J Atheroscler Thromb*. 2011;18(1):49-55.
357. Leeson P. Hypertension and cardiovascular risk in young adult life: insights from CAVI. *Eur Heart J Suppl*. 2017;19(Suppl B):B24-B9.
358. Zeisler H, Llorba E, Chantraine F, Vatish M, Staff AC, Sennstrom M, et al. Soluble fms-Like Tyrosine Kinase-1-to-Placental Growth Factor Ratio and Time to Delivery in Women With Suspected Preeclampsia. *Obstet Gynecol*. 2016;128(2):261-9.
359. Vatish M, Strunz-McKendry T, Hund M, Allegranza D, Wolf C, Smare C. The sflt-1/plgf ratio test in pre-eclampsia: an economic assessment for the UK. *Ultrasound Obstet Gynecol*. 2016.
360. Frampton GK, Jones J, Rose M, Payne L. Placental growth factor (alone or in combination with soluble fms-like tyrosine kinase 1) as an aid to the assessment of women with suspected pre-eclampsia: systematic review and economic analysis. *Health Technol Assess*. 2016;20(87):1-160.
361. National Institute for Health and Care Excellence. NICE Diagnostics Guidance 23: PIGF-based testing to help diagnose suspected pre-eclampsia (Triage PIGF test, Elecsys immunoassay sFlt-1/PIGF ratio, DELFIA Xpress PIGF 1-2-3 test, and BRAHMS sFlt-1 Krypton/BRAHMS GF plus Kryptor PE ratio). 2016.
362. Thadhani R, Kisner T, Hagmann H, Bossung V, Noack S, Schaarschmidt W, et al. Pilot Study of Extracorporeal Removal of Soluble Fms-Like Tyrosine Kinase 1 in Preeclampsia. *Circulation*. 2011;124(8):940-50.

363. Fox KA, Longo M, Tamayo E, Kechichian T, Bytautiene E, Hankins GDV, et al. Effects of pravastatin on mediators of vascular function in a mouse model of soluble Fms-like tyrosine kinase-1-induced preeclampsia. *Am J Obstet Gynecol*. 2011;205(4):366.e1-e5.
364. Flamme I, Frolich T, Risau W. Molecular mechanisms of vasculogenesis and embryonic angiogenesis. *J Cell Physiol*. 1997;173(2):206-10.
365. Venkatesha S, Toporsian M, Lam C, Hanai J, Mammoto T, Kim YM, et al. Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nat Med*. 2006;12(6):642-9.
366. Mutter WP, Karumanchi SA. Molecular mechanisms of preeclampsia. *Microvasc Res*. 2008;75(1):1-8.
367. Franz MB, Burgmann M, Neubauer A, Zeisler H, Sanani R, Gottsauner-Wolf M, et al. Augmentation index and pulse wave velocity in normotensive and pre-eclamptic pregnancies. *Acta Obstet Gyn Scand*. 2013;92(8):960-6.
368. Baylis C. Glomerular filtration rate in normal and abnormal pregnancies. *Semin Nephrol*. 1999;19(2):133-9.
369. Arulkumaran N, Lightstone L. Severe pre-eclampsia and hypertensive crises. *Best Pract Res Clin Obstet Gynaecol*. 2013;27(6):877-84.
370. Hauth JC, Ewell MG, Levine RJ, Esterlitz JR, Sibai B, Curet LB, et al. Pregnancy outcomes in healthy nulliparas who developed hypertension. Calcium for Preeclampsia Prevention Study Group. *Obstet Gynecol*. 2000;95(1):24-8.
371. Vyakaranam S, Bhongir AV, Patlolla D, Chintapally R. Study of serum uric acid and creatinine in hypertensive disorders of pregnancy. *Int J Med Sci Public Health*. 2015;4(10):1424-8.
372. von Dadelszen P, Firoz T, Donnay F, Gordon R, Hofmeyr GJ, Lalani S, et al. Preeclampsia in low and middle income countries-health services lessons learned from the PRE-EMPT (PRE-Eclampsia-Eclampsia Monitoring, Prevention and Treatment) project. *J Obstet Gynaecol Can*. 2012;34(10):917-26.
373. Statistical bulletin: Births in England and Wales: 2015 (Live births, stillbirths, and the intensity of childbearing measured by the total fertility rate) 2016 [Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthsummarytablesenglandandwales/2015>].
374. von Dadelszen P, Magee LA, Payne BA, Dunsmuir DT, Drebit S, Dumont GA, et al. Moving beyond silos: How do we provide distributed personalized medicine to pregnant women everywhere at scale? Insights from PRE-EMPT. *Int J Gynaecol Obstet*. 2015;131(Suppl 1):S10-S5.
375. Isler CM, Barrilleaux PS, Rinehart BK, Magann EF, Martin JN, Jr. Postpartum seizure prophylaxis: using maternal clinical parameters to guide therapy. *Obstet Gynecol*. 2003;101(1):66-9.
376. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet*. 2006;367(9516):1066-74.
377. Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS, Shackelford KA, Steiner C, Heuton KR, et al. Global, regional, and national levels and causes of maternal mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384(9947):980-1004.

378. Royston G, Hagar C, Long LA, McMahon D, Pakenham-Walsh N, Wadhwani N, et al. Mobile health-care information for all: a global challenge. *Lancet Glob Health*. 2015;3(7):e356-e7.
379. Nathan HL, de Greeff A, Hezelgrave NL, Chappell LC, Shennan AH. An accurate semiautomated oscillometric blood pressure device for use in pregnancy (including pre-eclampsia) in a low-income and middle-income country population: the Microlife 3AS1-2. *Blood Press Monit*. 2015;20(1):52-5.
380. Payne BA, Hutcheon JA, Ansermino JM, Hall DR, Bhutta ZA, Bhutta SZ, et al. A risk prediction model for the assessment and triage of women with hypertensive disorders of pregnancy in low-resourced settings: the miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) multi-country prospective cohort study. *PLoS Med*. 2014;11(1).

Appendices

- [1] Publication of systematic review (*Chapter 2*)
- [2] Protocol for systematic review (*Chapter 2*)
- [3] Systematic review PRISMA statement (*Chapter 2*)
- [4] Publication of survey (*Chapter 3*)
- [5] Audit tool (*Chapter 3*)
- [6] GP questionnaire for audit (*Chapter 3*)
- [7] Protocol for survey (*Chapter 3*)
- [8] Survey participant information sheet (*Chapter 3*)
- [9] SNAP-HT blood pressure monitoring instructions (*Chapter 4*)
- [10] SNAP-HT Telemonitoring manual for patients (*Chapter 4*)
- [11] SNAP-HT Telemonitoring manual for research team (*Chapter 4*)
- [12] SNAP-HT Feasibility study protocol (*Chapter 4*)
- [13] SNAP-HT Patient facing documents (*Chapter 4*)
 - a. Advert
 - b. Participant information sheet
 - c. Informed consent form
 - d. SNAP-HT GP/CMW letter (intervention group)
 - e. SNAP-HT GP/CMW letter (control group)
- [14] SNAP-HT Statistical analysis plan (*Chapter 4*)
- [15] SNAP-HT CONSORT 2010 checklist (*Chapter 4*)
- [16] Qualitative semi-structured interview template (*Chapter 5*)

APPENDIX 1: Publication of systematic review

Cairns AE, Pealing L, Duffy JMN, Roberts N, Tucker KL, Leeson P, Mackillop LH, McManus RJ.
Postpartum management of hypertensive disorders of pregnancy: a systematic review. *BMJ Open*
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BMJ Open Postpartum management of hypertensive disorders of pregnancy: a systematic review

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ABSTRACT

Objectives Hypertensive disorders of pregnancy (HDP) affect one in ten pregnancies and often persist postpartum when complications can occur. We aimed to determine the effectiveness and safety of pharmacological interventions, other interventions and different care models for postpartum hypertension management.

Design A systematic review was undertaken. Nine electronic databases, including Medline, were searched from inception to 16 March 2017. After duplicate removal, 4561 records were screened. Two authors independently selected studies, extracted study characteristics and data, and assessed methodological quality.

Setting Randomised controlled trials, case-control studies and cohort studies from any country and healthcare setting.

Participants Postnatal women with HDP.

Interventions Therapeutic intervention for management of hypertension, compared with another intervention, placebo or no intervention.

Primary and secondary outcome measures Outcome data were collected for maternal mortality and severe morbidity; systolic, diastolic and mean arterial blood pressure (BP) control; and safety data. Secondary outcome data collected included the length of postnatal hospital stay and laboratory values.

Results 39 studies were included (n=2901). Results were heterogeneous in terms of intervention, comparison and outcome requiring a narrative approach. There were insufficient data to recommend any single pharmacological intervention. 18 studies reported calcium-channel blockers, vasodilators and beta-blockers lowered BP postpartum. 12 of these reported safety data. Limited data existed regarding management in the weeks following hospital discharge. Neither loop diuretics (three studies) nor corticosteroids (one study) produced clinical benefit. Uterine curettage significantly reduced BP over the first 48 hours postpartum (range 6–13 mm Hg) compared with standard care (eight studies), with safety data only reported by four of eight studies.

Conclusion There was insufficient evidence to recommend a particular BP threshold, agent or model of care, but three classes of antihypertensive appeared variably effective. Further comparative research, including robust safety data, is required. Curettage reduced BP, but without adequate reporting of harms, so it cannot currently be recommended.

Strengths and limitations of this study

- All types of intervention for the management of postpartum hypertension—medical, surgical and organisation of care—were eligible for inclusion in this review.
- Randomised controlled studies plus other experimental study designs (cohort studies, case-control studies and quasi-randomised studies) were included, and no limitations were imposed in terms of language or publication date, resulting in a comprehensive review.
- This review highlights significant evidence gaps, demonstrating that further comparative research is required, particularly to clarify postpartum antihypertensive selection.
- Although 39 studies were included, the majority had a high risk of bias such that the evidence provided by this review is of low quality.
- The 39 studies reported a broad range of heterogeneous outcomes, limiting meaningful comparison.

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) often persist following delivery,¹ and sometimes arise de novo postpartum.² In both scenarios adverse events can occur during this period. Approximately one-third of eclampsia occurs postpartum, nearly half beyond 48 hours after childbirth.^{3–5} Half of the women who sustain an intracerebral haemorrhage in association with pre-eclampsia do so following birth.⁶ Women may enter the postnatal period requiring large doses of antihypertensive medication, but the majority will be treatment-free by 3–6 months.^{1 7} This rapidly changing blood pressure (BP) poses a challenge in terms of appropriate antihypertensive selection and dose adjustment.

The National Institute for Health and Care Excellence (NICE) recommends frequent postnatal BP monitoring for women with both pre-eclampsia (every 1–2 days for 2 weeks) and gestational hypertension (at

least once between days 3 and 5).⁸ The guideline stipulates thresholds for the increase or commencement ($\geq 150/100$ mm Hg) and the reduction or cessation (consider $< 140/90$ mm Hg and reduce $< 130/80$ mm Hg) of antihypertensive medication after birth. However, little detail is provided about frequency or proportion of dose reduction or how to manage multiple medications.⁸ The American College of Obstetricians and Gynecologists recommends that BP be monitored in hospital (or with an equivalent level of outpatient surveillance) for 72 hours after birth, and checked again 7–10 days postpartum (sooner if a woman is symptomatic).⁹ In line with NICE, they propose treating BP when $\geq 150/100$ mm Hg, but add this should be on two measures, 4–6 hours apart. They make no suggestion regarding BP thresholds for medication reduction, implying uncertainty about when to decrease or stop treatment.

A Cochrane review (search date January 2013) evaluated medical interventions for prevention and treatment of postnatal hypertension. This was limited to randomised controlled trials (RCTs) and included only nine studies.¹⁰ Given the paucity of evidence available, due to Cochrane's restriction to randomised trials alone, we have undertaken an updated systematic review of the postpartum management of hypertension in women with HDP with a broader scope, including the full range of interventions studied, and incorporating cohort and case-control studies, alongside RCTs. The following were our specific questions: (1) How should BP be monitored in women with HDP postpartum? (2) What BP thresholds should be used for antihypertensive treatment initiation, adjustment and cessation postpartum? (3) Which antihypertensive medication(s) should be used in postpartum in women with HDP? (4) What are the benefits and harms of other therapeutic interventions for women with HDP postpartum?

MATERIALS AND METHODS

A protocol, with explicitly defined objectives, study selection criteria, and approaches to assessing study quality, outcomes and statistical methods, was developed (online supplementary appendix S1). This was registered with PROSPERO: International Prospective Register of Systematic Reviews (CRD42015015527) and is available online (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015015527). We followed the guidelines for meta-analyses and systematic reviews outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (online supplementary appendix S2).¹¹

A systematic literature review was undertaken to capture evidence from human studies regarding postpartum hypertension management in women with HDP, without restriction by language or publication date (online supplementary appendix S1). We searched the following databases, from inception to 16 March 2017: Cochrane Database of Systematic Reviews, Database of Abstracts

of Reviews of Effects and Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, Embase, Medline, PsycINFO, Science Citation Index, Science (Web of Science Core Collection), Social Science Citation Index and Conference Proceedings Citation Index. We hand-searched reference lists and contacted relevant experts for potentially relevant studies, which might have been missed by electronic searches.¹²

We included RCTs, quasi-randomised studies, case-control studies, and prospective and retrospective cohort studies assessing interventions for hypertension management postpartum in women with HDP (gestational hypertension, pre-eclampsia, chronic hypertension and superimposed pre-eclampsia) arising both during pregnancy and de novo in the postnatal period. Consistent with guidance from Cochrane, conference abstracts were included.⁵

Two reviewers (AEC/LP) independently screened the titles and abstracts, and then critically reviewed the full text of selected studies to assess eligibility. Discrepancies were resolved by discussion before independent extraction of relevant data by the two reviewers. For trials with multiple intervention arms, we extracted data from eligible comparison arms. Data were extracted for the primary and secondary outcomes outlined in [table 1](#). Due to the heterogeneous nature of these studies, a narrative synthesis was undertaken.

Two reviewers (AEC/LP) independently assessed each trial's methodological quality using the Cochrane Collaboration's tool for assessing the risk of bias in RCTs,¹³ and the Newcastle-Ottawa Scale for case-control and cohort studies.¹⁴ A global assessment of bias across trials was made.

RESULTS

Our searches yielded 7105 records, and after excluding duplicates 4561 titles and abstracts were screened ([figure 1](#)). Eighty full-text articles were assessed: 35 articles were excluded (online supplementary appendix S3). Forty-five articles, representing 39 studies (32 randomised trials, 2 prospective cohort studies and 5 retrospective cohort studies) reporting data from 2901 postnatal participants, met our inclusion criteria (online supplementary appendix S4). Of the 39 studies, 9 (23%) were published only as conference abstracts. No further details were made available following author contact.

A range of interventions were assessed, including antihypertensive medications (18 studies, $n=982$), loop diuretics (4 studies, $n=503$), parenteral steroids (1 study, $n=157$), other medications (6 studies, $n=188$), uterine curettage (8 studies, $n=837$) and novel models of care (2 studies, $n=234$). Of the 39 studies, 9 (23%) included ≥ 100 participants, and only 2 studies included ≥ 200 participants.^{15 16} Four were from lower middle-income settings^{15 17–19} (classified according to the United Nations²⁰), and 13/39 (33%) studies had follow-up periods longer than 7 days

**Table 1** Outcome measures

	Outcome measures	Timing
Primary outcome(s)	Maternal mortality Maternal morbidity (ischaemic stroke, intracranial haemorrhage, eclamptic seizure; development of pre-eclampsia with severe features; postnatal complication requiring intervention) Systolic blood pressure control Diastolic blood pressure control Mean arterial pressure control Safety data (adverse events or maternal side effects)	Direct maternal deaths up to day 42 postpartum; late maternal deaths up to 1 year postpartum
Secondary outcome(s)	Critical care admission Length of hospital stay following delivery Postnatal readmission to secondary care Antihypertensive medication requirement Urine output Laboratory values Other as defined by study	

(online supplementary appendix S4). Only 5/39 (13%) and 7/39 (18%) studies, respectively, reported maternal mortality or major maternal morbidity, and while the majority of studies did report some measure of BP control, three did not (table 2A,B). Of the 39 studies, 19 (49%) reported safety data (table 2A,B).

Of the 39 studies, 5 (13%) studies (all evaluating antihypertensive medications) involved mixed antenatal and postnatal populations.^{17 21–24} Authors were contacted to request their data set for the postnatal participants, but no data were made available. Of the 39 studies, 6 (15%) included participants with chronic hypertension alongside women with de novo HDP (gestational hypertension or pre-eclampsia).^{22 23 25–31} Twelve of 39 (31%) included women with eclampsia—in one, all participants were eclamptic (online supplementary appendix S5).¹⁷

Thirty of 32 (94%) included RCTs were judged to be at high overall risk of bias, by both reviewers, according to the Cochrane tool, 23/32 (72%) for multiple domains. Only 2 of 32 (6%) were thought to be clearly at low risk of bias.^{29–32} All included cohort studies were deemed to have a high risk of bias in at least one domain of the Newcastle-Ottawa Scale (online supplementary appendix S6).

How should BP be monitored postpartum in women with HDP?

No studies specifically addressed the frequency or method of postnatal BP monitoring. Two evaluated the impact of postpartum care organisation (n=234), using the postnatal readmission rate as their primary outcome (online supplementary appendix S4). Neither reported maternal mortality or morbidity, safety data nor any measure of BP control (table 2B).^{26 33}

One assessed introduction of a specialised postpartum clinic (no further details were given) and demonstrated an increased postnatal readmission and triage visit rate (22% intervention group, 9% control group: difference 13%, $P<0.04$), although 86% occurred before a participant was seen in the clinic.³³ The second study evaluated specialist nurse follow-up, including home visits and

telephone contact, and reported no significant difference in the postnatal readmission rate compared with standard care.²⁶

What BP thresholds should be used for antihypertensive treatment initiation, adjustment and cessation postpartum?

No relevant studies identified.

Which antihypertensive medication(s) should be used postpartum in women with HDP?

Fourteen randomised trials (n=645), one quasi-randomised trial (n=15) and three retrospective cohort studies (n=322) evaluated antihypertensive medications (online supplementary appendix S4). Only three studies reported maternal mortality,^{29–31 34 35} and three reported maternal morbidity; no differences between groups were reported (table 2A).^{29–31 35 36} Twelve studies reported safety data, in comparisons between multiple classes of antihypertensive agents (table 2A); no clear differences were established, although one study found a greater number of minor side effects reported with oral nifedipine than with oral labetalol.^{27 28}

The vast majority of included studies evaluated either acute control of severe hypertension (7/18, 39%) or BP control in the few days after delivery and while women remained hospital inpatients (8/18, 44%). Only three studies, two published only as conference abstracts, evaluated BP control in the weeks and months following hospital discharge.^{25 27 28 37}

Calcium-channel blockers

Three small studies examined oral nifedipine (n=135); nifedipine resulted in a greater decrease in mean arterial pressure (MAP) 18–24 hours after childbirth than placebo (intervention group 93.9±1.6 mm Hg, control group 100.2±2.6 mm Hg; difference 6.3 mm Hg, $P<0.05$), but not at other time points to 48 hours (one RCT, n=31).³² Nifedipine controlled severe hypertension to <160/100 mm Hg more quickly than labetalol (intervention group

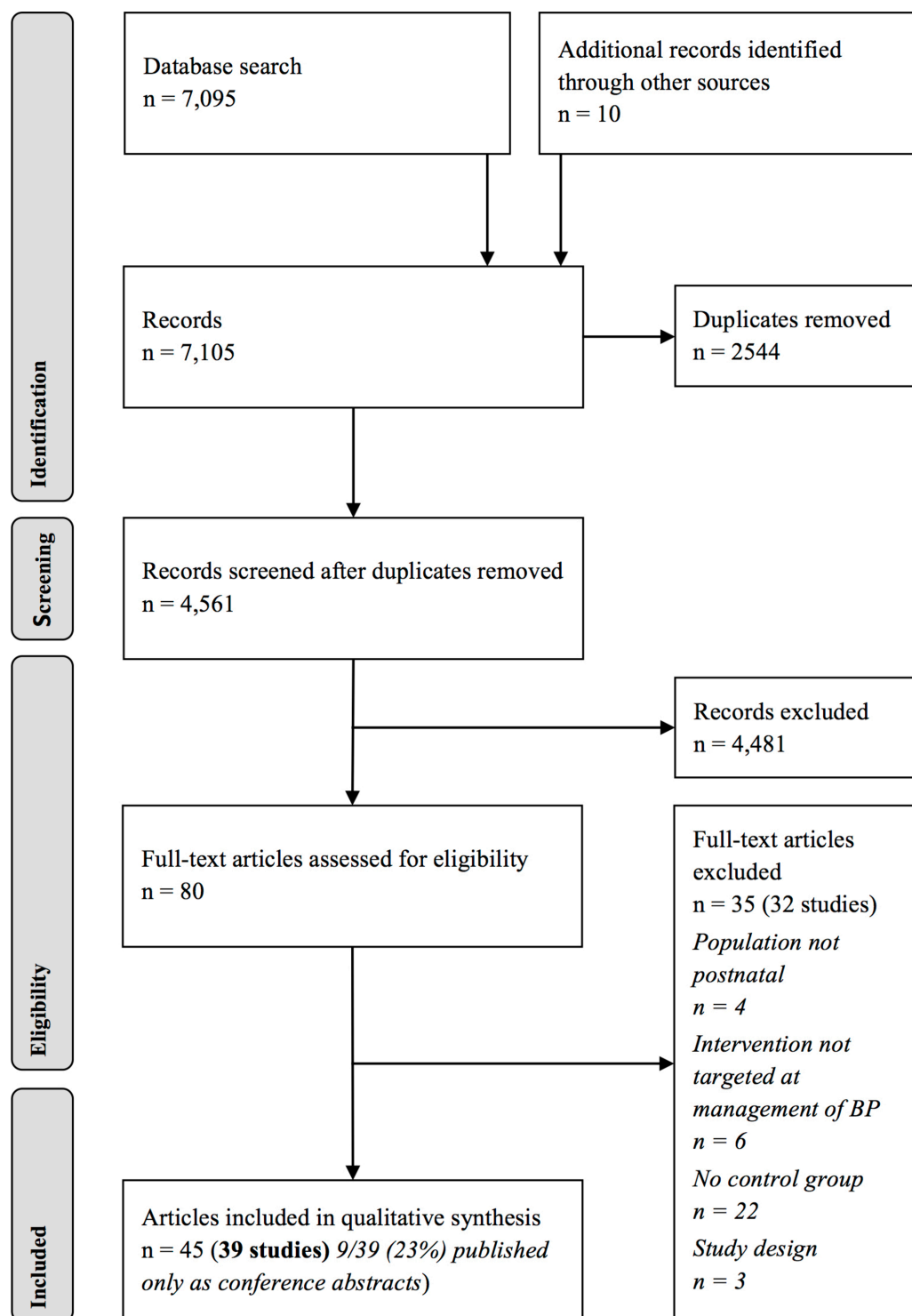


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart. BP, blood pressure.

25.1±13.6 min, control group 43.6±25.4 min: difference 18.5 min, $P=0.002$; one RCT, $n=21$).²¹ A single RCT ($n=83$) reported no significant difference in time taken to control BP to <150/100 mm Hg when comparing nifedipine with methyldopa.³⁴

Vasodilators

Six studies looked at the use of vasodilators ($n=252$). All used hydralazine via a range of administration routes.

Bolus intravenous hydralazine controlled severe hypertension more quickly than continuous infusion (intervention group 65.23±23.38 min, control group 186.36±79.77 min: difference -121.13 min, $P<0.001$; one quasi-randomised study, $n=15$ (postnatal)).¹⁷ Intramuscular hydralazine produced a more significant improvement in MAP at 6 hours than intravenous methyldopa (intervention group 104.5 mm Hg, control group 112 mm Hg: difference -7.5 mm Hg, $P=0.0057$) but not at other time points

Table 2 Primary outcome and safety data reporting in included studies

Study ID	Intervention	Control	Primary outcome assessment					Safety data reporting	Results (for reported outcomes)	
			Maternal mortality	Maternal morbidity	SBP control	DBP control	MAP control			
(A) Antihypertensive medications, 18 studies										
Calcium-channel blockers (three studies)										
Barton <i>et al</i> ³²	Nifedipine (oral)	Placebo								SBP control: no significant difference DBP control: no significant difference MAP control: improved in intervention group (difference 6.3mm Hg, P<0.05)
Vermillion <i>et al</i> ²¹	Nifedipine (oral)	Labetalol (intravenous bolus)								SBP control: improved in intervention group (difference in time to target BP 18.5 min, P=0.002) DBP control: improved in intervention group (difference in time to target BP 18.5 min, P=0.002) Safety: no significant difference; 1/25 intervention group became hypotensive
Sayin <i>et al</i> ³⁴	Nifedipine (oral)	Methyldopa (oral)								Maternal mortality: no significant difference SBP control: no significant difference DBP control: no significant difference
Vasodilators (6 studies)										
Palot <i>et al</i> ³⁶	Hydralazine (intravenous infusion) plus furosemide (intravenous bolus)	Clonidine (intravenous) plus furosemide (intravenous bolus)								Maternal morbidity: no statistical analysis
Griffis <i>et al</i> ^{38 39}	Hydralazine (intramuscular)	Methyldopa (intravenous bolus)								MAP control: no significant difference Safety: no significant difference; no side effects reported in either group
Walss Rodriguez <i>et al</i> ⁴⁰	Hydralazine (oral) plus nifedipine (oral, as required)	Nifedipine (oral, as required)								SBP control: no significant difference DBP control: no significant difference
Begum <i>et al</i> ¹⁷	Hydralazine (intravenous bolus)	Hydralazine (intravenous infusion)								DBP control: improved in intervention group (difference in time to target DBP 121.1 min, P<0.001) Safety: no significant difference; no side effects reported in either group
Vigil-De Gracia <i>et al</i> ³⁵	Hydralazine (intravenous bolus)	Labetalol (intravenous bolus)								Maternal mortality: no significant difference Maternal morbidity: no significant difference SBP control: no significant difference DBP control: no significant difference Safety: no significant difference; small numbers of side effects reported in both groups

Continued

Table 2 Continued

Study ID	Intervention	Control	Primary outcome assessment				Safety data reporting	Results (for reported outcomes)
			Maternal mortality	Maternal morbidity	SBP control	DBP control	MAP control	
Hennessy <i>et al</i> ²³	Diazoxide (intravenous bolus)	Hydralazine (intravenous bolus)			●	●		SBP control: improved in intervention group (difference in percentage achieving target BP 23%, P<0.01) DBP control: improved in intervention group (difference in percentage achieving target BP 23%, P<0.01)
Beta-blockers (5 studies)								
Garden <i>et al</i> ²⁴	Labetalol (intravenous infusion)	Dihydralazine (intravenous infusion)				●	●	DBP control: no statistical analysis Safety: no statistical analysis; 1/6 intervention group developed bronchospasm; 4/6 control group developed tachycardia and 1/6 developed oliguria; 4/6 control group, drug stopped due to a precipitous fall of DBP to 40–50 mm Hg
Fidler <i>et al</i> ⁴²	Timolol (oral)	Methyldopa (oral)			●	●		SBP control: improved in intervention group (difference 5.1 mm Hg, P<0.05) DBP control: no significant difference Safety: no statistical analysis; 1/40 intervention group became disorientated; 1/40 control group became hypotensive and 1/40 became drowsy
Mabie <i>et al</i> ²²	Labetalol (intravenous bolus)	Hydralazine (intravenous bolus)					●	MAP control: improved in control group (difference 7.8 mm Hg, P=0.02) Safety: no statistical analysis; 1/40 intervention group developed scalp tingling; 2/20 control group developed headaches
Shumard <i>et al</i> ⁴¹	Labetalol (oral)	Nifedipine (oral)			●	●	●	SBP control: improved in control group (difference in time to achieve target BP 1 day, P=0.0031) DBP control: improved in control group (difference in time to achieve target BP 1 day, P=0.0031)
Sharma <i>et al</i> ^{27 28}	Labetalol (oral)	Nifedipine (oral)			●	●	●	SBP: no significant difference DBP: no significant difference Safety: no major side effects reported in either group; minor side effects more commonly reported in control group (20% intervention, 48% control, P=0.04)
Thiazides (2 studies)								
Gaisin <i>et al</i> ²⁵	Indapamide (oral)	Methyldopa (oral)			●	●	●	SBP control: no significant difference DBP control: no significant difference Safety: no statistical analysis, no details reported
Ishat Gaisin <i>et al</i> ³⁷	Indapamide (oral) plus ursodeoxycholic acid (oral)	Methyldopa (oral)			●	●	●	SBP control: no significant difference DBP control: no significant difference Safety: no significant difference; no adverse events reported in either group
Indole alkaloids (1 study)								

Continued



Table 2 Continued

Study ID	Intervention	Control	Primary outcome assessment				Safety data reporting	Results (for reported outcomes)
			Maternal mortality	Maternal morbidity	SBP control	DBP control		
Krebs ^{43 44}	Reserpine (oral or intramuscular)	Phenobarbital			●	●	●	SBP control: no statistical analysis DBP control: no statistical analysis Safety: no statistical analysis; no adverse events reported in intervention group, no comment on control
Centrally acting alpha agonists (1 study)								
Noronha Neto <i>et al</i> ²⁹⁻³¹	Clonidine (oral)	Captopril (oral)	●	●	●	●	●	Maternal mortality: no significant difference Maternal morbidity: no significant difference SBP control: improved in intervention group (difference in number of episodes of high BP (1.4, P<0.08) DBP: improved in intervention group (difference in number of episodes of high BP (1.4, P<0.08) Safety: no significant difference; adverse reactions 18.6% intervention, 28.8% control, P=NS
(B) Loop diuretics, other drugs, uterine curettage and organisation of care, 21 studies								
Loop diuretics (4 studies)								
Matthews <i>et al</i> ⁴⁶	Furosemide (oral)	Placebo					●	MAP control: no significant difference
Ascarelli <i>et al</i> ¹⁶	Furosemide (oral)	No intervention	●	●	●	●	●	Maternal morbidity: no significant difference SBP control: no significant difference DBP control: no significant difference
Amorim <i>et al</i> ⁴⁵	Furosemide (oral)	Placebo		●	●	●	●	SBP control: improved in intervention group (difference not stated, P<0.001) DBP control: improved in intervention group (difference not stated, P<0.001) MAP control: improved in intervention group (difference not stated, P<0.001)
Veena <i>et al</i> ¹⁹	Furosemide (oral)+nifedipine (oral)	Nifedipine (oral)	●	●	●	●	●	Maternal morbidity: no significant difference SBP control: no significant difference DBP control: no significant difference MAP control: no significant difference
Other drugs (7 studies)								
Selective 5-HT antagonists								
Weiner ⁴⁸	R41468 (intravenous infusion)	Placebo					●	MAP control: improved in intervention group (difference 25.6mm Hg, P<0.001)

Continued

Table 2 Continued

Study ID	Intervention	Control	Primary outcome assessment				Safety data reporting	Results (for reported outcomes)
			Maternal mortality	Maternal morbidity	SBP control	DBP control	MAP control	
Weiner <i>et al</i> ⁴⁹	Ketanserin (intravenous infusion)	Placebo			●	●	●	SBP control: improved in intervention group (difference in SBP decline 34 mm Hg, P<0.001) DBP control: improved in intervention group (difference in DBP decline 27 mm Hg, P<0.001) MAP control: improved in intervention group (difference not stated, P<0.001) Safety: no statistical analysis; 3/20 intervention group experienced blurred vision, 1 of these was hypotensive (responded to hydration); 1/20 intervention group experienced mild euphoria
Montenegro <i>et al</i> ⁵⁰	Ketanserin (intravenous bolus+/- infusion)	Placebo			●	●	●	SBP control: improved in intervention group (absolute difference not stated, P<0.001) DBP control: improved in intervention group (absolute difference not stated, P<0.001) MAP control: improved in intervention group (absolute difference not stated, P<0.001)
Alternative therapies								
Hladunewich <i>et al</i> ⁵¹	L-arginine (oral or intravenous bolus)	Placebo			●	●	●	SBP control: no significant difference DBP control: no significant difference MAP control: no significant difference Safety: no significant difference; no adverse events reported in either group
Liu <i>et al</i> ⁵²	Shengkangbao (oral or intravenous bolus)	No intervention			●	●		SBP control: no significant difference DBP control: no significant difference
Steroids								
Barrilleaux <i>et al</i> ^{53 54}	Dexamethasone (intravenous bolus)	Placebo					●	MAP control: no significant difference
Atrial natriuretic peptide								
Shigemitsu <i>et al</i> ⁴⁷	Carperitide (route not specified)	No intervention	●				●	Maternal mortality: no significant difference MAP control: no significant difference Safety: no significant difference; no adverse events reported in either group
Uterine curettage (8 studies)								
Salvatore <i>et al</i> ⁵⁸	Uterine curettage	No intervention	●	●	●	●		Maternal morbidity: no statistical analysis SBP control: no statistical analysis DBP control: no statistical analysis

Continued



Table 2 Continued

Study ID	Intervention	Control	Primary outcome assessment				Safety data reporting	Results (for reported outcomes)
			Maternal mortality	Maternal morbidity	SBP control	DBP control	MAP control	
Magann <i>et al</i> ⁶⁹	Uterine curettage	No intervention					●	MAP control: improved in intervention group (difference at different time points to 24 hours postpartum 6–10 mm Hg, $P<0.05$) Safety: no significant difference; no complications reported from intervention (follow-up to 7 weeks postpartum)
Magann <i>et al</i> ⁶⁰	Uterine curettage	Nifedipine (oral) or no intervention					●	MAP control: no significant difference between intervention and oral nifedipine; improved in intervention group compared with no intervention (difference at 8–48 hour postpartum 9–13 mm Hg, $P=0.0017$) Safety: no significant difference; no complications/ side effects reported from interventions (follow-up to 7 weeks postpartum)
Gocmen <i>et al</i> ⁶⁷	Uterine curettage	No intervention					●	MAP control: improved in intervention group (difference not stated, $P=0.01$)
Gomez <i>et al</i> ⁶¹	Uterine curettage	No intervention					●	MAP control: improved in intervention group (difference not stated, $P<0.001$) Safety: no significant difference; no complications reported from intervention
Alkan <i>et al</i> ⁶²	Uterine curettage	No intervention					●	MAP control: improved in intervention group (difference 6.8 mm Hg, $P<0.05$) Safety: no significant difference; no complications reported from intervention
Ragab <i>et al</i> ¹⁵	Uterine curettage	No intervention	●	●			●	Maternal mortality: no significant difference Maternal morbidity: no statistical analysis MAP control: improved in intervention group (difference at 6 hour postpartum 12.3 mm Hg, $P=0.02$; difference at 24 hours postpartum, 9.2 mm Hg, $P=0.01$)
Mallapur <i>et al</i> ¹⁸	Uterine curettage	No intervention					●	MAP control: improved in intervention group (difference at 4 hour postpartum 7.6 mm Hg, $P<0.001$).
Organisation of care (2 studies)								
York <i>et al</i> ²⁶	Nurse specialist follow-up	No intervention						NA
Bibbo <i>et al</i> ³³	Specialist postpartum clinic	No intervention						NA

For primary outcome assessment where there was a significant difference between groups, the magnitude of the difference is reported; where any adverse events or side effects were reported, this is presented.

●=improved in intervention group; ●=no significant difference; ●=improved in control group; ●=unclear.

5-HT, 5-hydroxytryptamine; BP, blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; NA, not applicable; NS, non-significant; SBP, systolic blood pressure.

to 24 hours (one RCT, n=26).^{38 39} There was no difference in BP control when comparing oral hydralazine with oral nifedipine (one RCT, n=38) or intravenous labetalol (one RCT, n=82).^{35 40}

Bolus diazoxide was significantly more effective in achieving a target BP of $\leq 140/90$ mm Hg than intravenous hydralazine (intervention group 67%, control group 43%; relative risk (RR) 0.64, 95% CI 0.46 to 0.89; one RCT, n=37 (postnatal)).²³ One retrospective cohort study did not present any statistical analysis.³⁶

Beta-blockers

Five studies assessed the efficacy of beta-blockers (four RCTs and one retrospective cohort study, n=305). Two RCTs compared intravenous labetalol with intravenous hydralazine/dihydralazine; one involved only six postnatal women and presented no statistical analysis of the data.²⁴ The other found a significantly greater mean maximal decrease in MAP with intravenous labetalol (intervention group 25.5 ± 11.2 mm Hg, control group 33.3 ± 13.2 mm Hg; difference -7.8 mm Hg, $P=0.02$; one RCT, n=32 (postnatal)).²² Results conflicted regarding whether oral labetalol was more or less effective than oral nifedipine; a cohort study reported that labetalol controlled BP less rapidly than nifedipine (intervention group 2.7 days, control group 1.7 days; difference 1.0 days, $P=0.0031$; one retrospective cohort study, n=128).⁴¹ However, this result was not replicated by an RCT, where the time to BP control was similar in the two groups (n=50).^{27 28} Neither study demonstrated a difference in the postnatal length of stay (n=178). Timolol was effective in decreasing diastolic BP on the first day postnatal when compared with methyldopa (intervention group 88.7 mm Hg, control group 93.8 mm Hg; difference -5.1 mm Hg, $P<0.05$; one RCT, n=80).⁴²

Other antihypertensive medications

No statistically significant difference was found between oral clonidine and oral captopril in the incidence of episodes of severe hypertension postpartum (one RCT, n=90).^{29–31} Two RCTs evaluating indapamide versus methyldopa found no difference in BP control over 6–12 months postpartum (n=60).^{25 37} One retrospective cohort study (n=140) compared reserpine with phenobarbital; the results suggested that reserpine might achieve faster and greater BP reduction (data extracted from graphs; no statistical analysis). No adverse events were reported in the intervention group.^{43 44}

What are the benefits and harms of other therapeutic interventions for women with HDP postpartum?

Loop diuretics

Four RCTs (n=503) examined loop diuretics versus placebo or usual care in postpartum hypertension management in women with HDP. None reported maternal mortality or safety data. Only two reported major maternal morbidity, neither demonstrating a difference between groups (table 2B).^{16 19}

One RCT (n=120) reported significant improvement in the primary outcome of mean systolic and diastolic BP with oral furosemide versus placebo (magnitude of difference or time points of measurements not stated, $P<0.001$).⁴⁵ This was not the case in the other placebo-controlled RCT, which found no significant difference (n=19).⁴⁶ Two further RCTs (n=364) found no significant difference in BP control with oral furosemide versus usual care.^{16 19} In one of these, subgroup analysis of women with severe pre-eclampsia (n=70) found women who received oral furosemide had a significantly lower systolic BP at day 2 postpartum (intervention group 142 ± 13 mm Hg, control group 153 ± 19 mm Hg; difference -11 mm Hg, $P<0.004$), but not at other time points.¹⁶ In the other trial (n=100), furosemide reduced the need for additional antihypertensive treatment during the 3 days of therapy (intervention group 8.0%, control group 26.0%; difference 18%, $P=0.017$), but this difference did not persist to hospital discharge.¹⁹

Other drugs

Five RCTs, one quasi-randomised study and one retrospective cohort study investigated the utility of different drug classes in HDP postpartum (online supplementary appendix S5). Three studies reported safety data, but only one reported maternal mortality, demonstrating no difference between groups,⁴⁷ and none reported major maternal morbidity (table 2B).

Three small, crossover RCTs examined the use of selective serotonin receptor inhibitors (SSRIs) compared with placebo (n=55). All studies showed a significant reduction in BP with SSRIs compared with placebo (range 25.6–34 mm Hg).^{48–50} These data suggest efficacy for this drug class in hypertension management but do not provide any information regarding relative effectiveness compared with standard antihypertensive drugs. Only one study reported safety data; although no statistical analysis was performed, there were a number of side effects reported in the intervention group.⁴⁹

Two studies evaluated alternative therapies (n=117); there was no difference in BP control with L-arginine supplementation compared with placebo (one RCT, n=45).⁵¹ One reported accelerated recovery of albuminuria with the administration of shengkangbao (Chinese herbal medicine) versus placebo (one quasi-randomised study, n=72). However, the clinical relevance of this outcome is uncertain; there was no difference between groups in the secondary outcomes of systolic BP, diastolic BP or serum creatinine, and no safety data were reported.⁵²

A single RCT assessed corticosteroids in the management of severe pre-eclampsia postpartum (n=157).^{53 54} No difference was demonstrated between groups in the primary outcome of antihypertensive medication requirement, or in the secondary outcomes of MAP or need for critical care admission, and no safety data were reported. There were small, statistically significant differences found in some laboratory values (platelet count, lactate dehydrogenase and aspartate transaminase). However,



the authors acknowledged that the absolute differences were too small to be clinically relevant.⁵³

A very small retrospective cohort study suggested an improvement in MAP with the addition of carperitide (atrial natriuretic peptide) to standard therapy (n=16), and no adverse effects related to the intervention were reported.⁴⁷ However, the magnitude of the difference was not published, and the study was too small to draw any firm conclusions.

Uterine curettage

Six RCTs and two prospective cohort studies (n=837) have explored the role of uterine curettage in postpartum hypertension management. Uterine curettage is a similar process to that used in the surgical management of miscarriage; the lining of the uterus is scraped after completion of the third stage of labour in order to maximise placental tissue removal. This may be under direct vision following caesarean section, or via the transcervical route following vaginal birth. The latter approach may be ultrasound-guided and necessitates some form of anaesthesia. The theory underlying this intervention is that gestational hypertension and pre-eclampsia are placenta-mediated, and therefore ensuring complete evacuation of the uterus following childbirth may accelerate recovery.^{55 56}

Seven studies explicitly stated they included both participants who delivered vaginally and those delivered by caesarean; four reported numbers undergoing vaginal delivery (n=248) and caesarean (n=321). One made no comment about the mode of birth.⁵⁷ Only one study reported maternal mortality, and there was no difference between groups.¹⁵ Two reported major maternal morbidity, but neither performed any statistical analysis (table 2B). However, both studies did suggest a reduction in the absolute number of eclamptic seizures in the curettage group compared with no intervention.^{15 58} In one, however, there was a relevant difference between the study groups; 28/28 (100%) in the control group were eclamptic at enrolment, compared with 9/20 (45%) in the intervention group.⁵⁸ Four studies reported safety data, with none reporting any complications related to the intervention (table 2B).⁵⁹⁻⁶²

All eight studies compared curettage with standard care (ie, no additional intervention), and all suggested that uterine curettage resulted in a significantly lower BP.^{15 18 57-62} One of these had two control groups: standard care and oral nifedipine; when compared with oral nifedipine, no difference was noted with curettage.⁶⁰

Five studies reported the magnitude of the difference in MAP between curettage and standard care: range 6-13 mm Hg.^{15 18 59 60 62} Only two of these reported BP data beyond 24 hours postpartum; one RCT reported a significantly lower MAP at 48 hours with curettage (intervention group 104 mm Hg, control group 113 mm Hg; difference 9 mm Hg, P=0.0017; n=45),⁶⁰ but the other RCT demonstrated no significant difference in MAP at 48 hours (n=420).¹⁵

One study demonstrated that a greater proportion of the intervention group attained the target BP of <140/90 mm Hg at 24 (intervention group 9/20 (45%), control group 3/28 (11%); difference 34%, no P value quoted) and 48 hours postpartum (intervention group 14/20 (70%), control group 8/28 (29%); difference 41%, no P value quoted).⁵⁸ Two studies did not present the size of the difference between groups.^{57 61}

DISCUSSION

This review found evidence demonstrating that calcium-channel blockers, vasodilators and beta-blockers lower BP postpartum, but no clear answer to which was most effective and should, therefore, be preferentially prescribed. All but two studies examined the acute control of severe hypertension or short-term BP control while women remained in hospital postpartum,^{25 37} and so provide little guidance about prescription in the weeks after discharge. Moreover these both examined thiazide diuretics, not recommended in the UK for use while breast feeding.⁸ Complete safety data were limited across trials, as were data regarding objective clinical outcomes, and two further studies examined antihypertensive agents not recommended for use postpartum in the UK (methyldopa and reserpine).^{63 64} One trial evaluated captopril at a much higher daily dose than the UK recommended daily starting dose.⁶⁴

Uterine curettage is not currently recommended, due to safety concerns regarding additional anaesthetic and operative risks, and the availability of alternative treatments to lower BP, particularly in the context of vaginal birth.⁶⁵ However, the included studies consistently demonstrated that uterine curettage improved BP control versus standard care,^{15 18 57-62} with one reporting an equivalent effect to oral nifedipine.⁶⁰ Among the limited safety data, none reported an excess complication rate (infection or uterine damage) with curettage, but given the low incidence of operative complications, the total population (n=837) was likely insufficient to adequately address potential competing risks. Furthermore, these studies did not demonstrate any impact from curettage on maternal mortality or severe morbidity, and concerns exist about some studies' methodology. The evidence reviewed is insufficient to recommend incorporation of this intervention into routine clinical practice.

Four trials evaluating loop diuretics failed to provide conclusive evidence of benefit. Three produced non-significant results in their main analysis,^{16 19 46} and the single conference abstract, which did suggest better BP control with oral furosemide, did not publish the magnitude of the difference, rendering it difficult to assess the clinical relevance.⁴⁵ In contrast to the Cochrane review, we conclude that, at present, there is no evidence to support the routine use of diuretics postpartum.¹⁰

We found no adequate evidence to support alternative medications or a particular care model in the management of HDP postpartum. SSRIs substantially reduced BP

versus placebo,^{48–50} but no published data were identified comparing their efficacy with standard antihypertensive treatment, making it difficult to draw meaningful conclusions about their clinical application. Neither study evaluating postpartum care organisation reported maternal mortality or morbidity, or any measure of BP control, with both selecting postnatal readmissions as their primary outcome. An increased postnatal readmission rate, however, may not necessarily reflect harm; it might instead suggest that a particular model of care can better detect problems in the community and admit appropriately, ultimately resulting in a lower risk to patients.

In light of the heterogeneous nature of research in this field, when designing this review, we included all interventions targeting hypertension management, but not end-organ complications, including eclampsia. Therefore, trials evaluating magnesium sulfate were outside the scope of this review. We acknowledge the relevance of this therapy in women with severe pre-eclampsia, especially in the immediate postnatal period, and a Cochrane review suggests there is no uncertainty regarding the effectiveness of this therapy.⁶⁶

A strength of this review is that cohort studies, case-control studies and quasi-randomised studies were eligible in addition to RCTs, and no language or date restrictions were imposed, resulting in a comprehensive review that provides evidence suggesting significant research gaps, consistent with the findings from the Cochrane review (2013).¹⁰ The applicability of the findings and recommendations from this review is restricted by the low quality of included studies; both reviewers judged the vast majority to be at high overall risk of bias. Nearly a quarter of the included studies were published only as conference abstracts, and therefore not subjected to peer review. Data extraction was restricted to the information provided in the abstracts (no authors provided additional data on request). These were limiting factors in our analysis, but we nonetheless felt it was important to include these studies for completeness, especially given the paucity of evidence that exists in this field. A further justification for their inclusion is that half of the trials reported in conference abstracts never reach full publication, and positive trials are more likely to be published than negative ones,⁶⁷ which has the potential to skew the results of a review if they are omitted.

A further limitation of this review is that the majority of identified studies did not report substantive clinical outcomes such as maternal mortality, morbidity or harms. Without these, it is difficult to define properly the potential role of proposed interventions in clinical practice. The incidence of adverse maternal and neonatal outcomes, particularly in high-resource settings, is low, meaning adequately powering studies for real outcomes of interest is financially demanding. Therefore researchers often employ surrogate outcomes. Additionally, the range of outcomes reported in included studies was broad and inconsistent, with BP changes in particular being measured in a variety of different ways,

further limiting the comparability of trials. Increasingly, core outcome sets are being produced, with a view to trials reporting as standard a minimum set of outcomes that are clinically meaningful and important to patients.⁶⁸ We hope in the future that this would enhance our ability to synthesise results from different studies to produce high-quality evidence. There is consensus about trying to move away from surrogate outcomes, for example time to BP control, as they cannot effectively substitute for clinically important outcomes. An important and clinically meaningful end point should measure how a patient feels, functions or survives.

The Cochrane review included only nine randomised trials (author names in bold in online supplementary appendix S4). We believe our review adds to this, as an additional 30 studies are included (19 predating the Cochrane search, and 11 subsequent to it), providing a current and complete summary of all available research in the field. The contrast between the scales of the two reviews highlights a lack of high-quality evidence, despite a reasonably high number of research studies being conducted to answer the question about how hypertension should be managed postpartum in women with HDP. In future, studies need to be more robust and better designed to address the research questions adequately. Furthermore, in spite of these extensions, the body of evidence identified was substantially smaller than that underpinning antenatal hypertension management; 18 studies (n=982), not restricted to RCTs, evaluated antihypertensive medications postpartum. Furthermore, the size of all but a few individual studies was small. In comparison, a Cochrane review (2014) evaluating antihypertensive medication for mild to moderate hypertension in pregnancy included 49 RCTs (n=4723).⁶⁹ Moreover, the quantity and quality of evidence supporting the management of HDP are vastly less than that available for essential hypertension outside pregnancy, where individual RCTs commonly involve several thousand participants.⁷⁰

This review demonstrates a lack of good-quality evidence for postpartum hypertension management, emphasising the need for further RCTs directly comparing different antihypertensive agents, BP thresholds for medication adjustment and different models of care, with outcome measures other than postnatal readmissions. We believe the studies examining uterine curettage justify further research to evaluate clinically meaningful outcomes and procedural risks. It might be pragmatic to confine this to curettage at caesarean section, given concerns regarding surgical intervention after vaginal birth; an additional anaesthetic is not required; infection risk is lowered within a sterile surgical field compared with the transcervical route; and curettage under direct vision limits perforation risk. This might be beneficial in women with severe pre-eclampsia, where BP control during pregnancy has been challenging despite multiple medications.⁵⁵

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Contributors AEC drafted the protocol with JMND, and drafted and piloted the data extraction sheet. These were reviewed by RJMcM, LP, KLT, LHM and PL. NR and AEC wrote the search strategy, and the online searches were conducted by NR. AEC and LP reviewed the search results independently and carried out the data extraction. This manuscript was drafted by AEC and reviewed by RJMcM, JMND, LP, NR, KLT, LHM and PL. AEC will be the guarantor.

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REFERENCES

1. Podymow T, August P. Postpartum course of gestational hypertension and preeclampsia. *Hypertens Pregnancy* 2010;29:294–300.
2. Goel A, Maski MR, Bajracharya S, *et al.* Epidemiology and mechanisms of De Novo and persistent hypertension in the postpartum period. *Circulation* 2015;132:1726–33.
3. Chames MC, Livingston JC, Ivester TS, *et al.* Late postpartum eclampsia: a preventable disease? *Am J Obstet Gynecol* 2002;186:1174–7.
4. Kayem G, Kurinczuk JJ, Spark P, *et al.* Maternal and obstetric factors associated with delayed postpartum eclampsia: a national study population. *Acta Obstet Gynecol Scand* 2011;90:1017–23.
5. Watson DL, Sibai BM, Shaver DC, *et al.* Late postpartum eclampsia: an update. *South Med J* 1983;76:1487–9.
6. Martin JN, Thigpen BD, Moore RC, *et al.* Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. *Obstet Gynecol* 2005;105:246–54.
7. Berks D, Steegers EA, Molas M, *et al.* Resolution of hypertension and proteinuria after preeclampsia. *Obstet Gynecol* 2009;114:1307–14.
8. National Institute for Health and Care Excellence. *NICE clinical guideline 107: hypertension in pregnancy: the management of hypertensive disorders during pregnancy*, 2011.
9. ACOG Task Force on Hypertension in Pregnancy. *Hypertension in pregnancy: American college of obstetricians and gynecologists*, 2013.
10. Magee L, von Dadelszen P. Prevention and treatment of postpartum hypertension. *Cochrane Database Syst Rev* 2013;4.
11. Moher D, Shamseer L, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
12. McManus RJ, Wilson S, Delaney BC, *et al.* Review of the usefulness of contacting other experts when conducting a literature search for systematic reviews. *BMJ* 1998;317:1562–3.
13. Higgins JP, Altman DG, Gotzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
14. Wells GA, Shea B, O'Connell D, *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2017 http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm (accessed 14 Jul 2017).
15. Ragab A, Goda H, Raghib M, *et al.* Does immediate postpartum curettage of the endometrium accelerate recovery from preeclampsia-eclampsia? A randomized controlled trial. *Arch Gynecol Obstet* 2013;288:1035–8.
16. Ascarelli MH, Johnson V, McCreary H, *et al.* Postpartum preeclampsia management with furosemide: a randomized clinical trial. *Obstet Gynecol* 2005;105:29–33.
17. Begum MR, Quadir E, Begum A, *et al.* Management of hypertensive emergencies of pregnancy by hydralazine bolus injection vs continuous drip—a comparative study. *Medscape Womens Health* 2002;7:1.
18. Mallapur A, Renuka B, Katageri G, *et al.* Role of postpartum curettage in recovery of severe preeclampsia and eclampsia patients—a randomised controlled trial. *Int J Gynaecol Obstet* 2015;131:E191.
19. Veena P, Perivela L, Raghavan SS. Furosemide in postpartum management of severe preeclampsia: a randomized controlled trial. *Hypertens Pregnancy* 2017;36:84–9.
20. United Nations Department of Economic and Social Affairs. *World economic situation and prospects*. New York, United States of America: United Nations, 2016.
21. Vermillion ST, Scardo JA, Newman RB, *et al.* A randomized, double-blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy. *Am J Obstet Gynecol* 1999;181:858–61.
22. Mabie WC, Gonzalez AR, Sibai BM, *et al.* A comparative trial of labetalol and hydralazine in the acute management of severe hypertension complicating pregnancy. *Obstet Gynecol* 1987;70:328–33.
23. Hennessy A, Thornton CE, Makris A, *et al.* A randomised comparison of hydralazine and mini-bolus diazoxide for hypertensive emergencies in pregnancy: the PIVOT trial. *Aust N Z J Obstet Gynaecol* 2007;47:279–85.
24. Garden A, Davey DA, Dommissie J. Intravenous labetalol and intravenous dihydralazine in severe hypertension in pregnancy. *Clin Exp Hypertens B* 1982;1:371–83.
25. Gaisin IR, Iskhakova AS, Shilina LV. Indapamide in the management of post-partum hypertension: a randomized, case-control study. *Eur Heart J* 2013;34:P1426.
26. York R, Brown LP, Samuels P, *et al.* A randomized trial of early discharge and nurse specialist transitional follow-up care of high-risk childbearing women. *Nurs Res* 1997;46:254–61.
27. Sharma KJ, Greene N, Kilpatrick SJ. 40: Oral labetalol compared to oral extended release nifedipine for persistent postpartum hypertension: a randomized controlled trial. *Am J Obstet Gynecol* 2016;214:S27–8.
28. Sharma KJ, Greene N, Kilpatrick SJ. Oral labetalol compared to oral nifedipine for postpartum hypertension: a randomized controlled trial. *Hypertens Pregnancy* 2017;36:44–7.
29. Noronha Neto C C, Maia SS, Katz L, *et al.* Clonidine versus captopril for severe postpartum hypertension: a randomized controlled trial. *PLoS One* 2017;12:e0168124.
30. Amorim MMR, Noronha-Neto C, Maia SB, *et al.* Clonidine compared with captopril for severe postpartum hypertension. *Obstet Gynecol* 2015;125:42S.
31. Katz L, Noronha Neto C, Maia S, *et al.* Clonidine versus captopril for severe postpartum hypertension: a randomized controlled trial. *Pregnancy Hypertens* 2015;5:29–30.
32. Barton JR, Hiett AK, Conover WB. The use of nifedipine during the postpartum period in patients with severe preeclampsia. *Am J Obstet Gynecol* 1990;162:788–92.
33. Bibbo C, Celi A, Thomas AM, *et al.* Does the addition of a specialized postpartum clinic improve the care of women with preeclampsia? *Obstet Gynecol* 2014;123:39S.
34. Sayin NC, Altundag G, Varol FG. Efficacy of alpha-methyldopa and nifedipine in the treatment of postpartum hypertension. [Turkish] Postpartum hipertansiyon tedavisinde alfametildopa ve nifedipinin etkinligi. *J Turk Ger Gynecol Assoc* 2005;6:118–22.
35. Vigil-De Gracia P, Ruiz E, López JC, *et al.* Management of severe hypertension in the postpartum period with intravenous hydralazine or labetalol: a randomized clinical trial. *Hypertens Pregnancy* 2007;26:163–71.
36. Palot M, Jakob L, Decaux J. Arterial hypertension of labor and the post-partum period. [French] Les Hypertensions Arteriellles Du Travail Et Du Post-Partum. *Rev Fr Gynecol Obstet* 1979;74:173–6.
37. Ilshat Gaisin IR, Iskhakova AS, Shilina LV. Control of cardiovascular risk factors with ursodeoxycholic acid and indapamide in postpreeclamptic nursing mothers: Results from a randomized, case-control 1-year study. *Eur J Prev Cardiol* 2014;21:S120.
38. Griffis KR, Martin JN, Palmer SM, *et al.* Utilization of hydralazine or alpha-methyldopa for the management of early puerperal hypertension. *Am J Perinatol* 1989;6:437–41.
39. Martin JN, Griffis KR, Martin RW, *et al.* Early puerperal hypertension management: hydralazine vs methyldopa. *Clin Exp Hypertens B* 1988;8:431.
40. Walss Rodriguez RJ, Villarreal Ordaz F. [Management of severe pre-eclampsia in the puerperium. Comparative study of sublingual nifedipine and hydralazine]. *Ginecol Obstet Mex* 1991;59:207–10.

41. Shumard K, Yoon J, Huang C, *et al.* 718: Peripartum anti-hypertensive choice affects time to blood pressure control in treating hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2016;214:S378.
42. Fidler J, Smith V, De Swiet M. A randomized study comparing timolol and methyldopa in hospital treatment of puerperal hypertension. *Br J Obstet Gynaecol* 1982;89:1031–4.
43. Krebs A. [Experience with serpasil and luminal in the management of pregnancy-and puerperal toxemias]. *Gynaecologia* 1956;141:255–60.
44. Krebs A. [Tests of reserpine and phenobarbital in therapy of toxicosis of pregnancy and puerperium]. *Geburtshilfe Frauenheilkd* 1956;16:410–22.
45. Amorim M, Katz L, Cursino T, *et al.* Postpartum furosemide for accelerating recovery in women with severe preeclampsia: A randomized clinical trial. *Int J Gynaecol Obstet* 2015;131:E195.
46. Matthews G, Gornall R, Saunders NJ. A randomised placebo controlled trial of loop diuretics in moderate/severe pre-eclampsia, following delivery. *J Obstet Gynaecol* 1997;17:30–2.
47. Shigemitsu A, Akasaka J, Shigetomi H, *et al.* Use of carperitide for postpartum diuresis of severe preeclampsia. *Pregnancy Hypertens* 2015;5:145.
48. Weiner CP, Serotonin SML. 5HT) receptor blockade in puerperal pre-eclampsia. *Clin Exp Hypertens B* 1982;1:195.
49. Weiner CP, Socol ML, Vaisrub N. Control of preeclamptic hypertension by ketanserin, a new serotonin receptor antagonist. *Am J Obstet Gynecol* 1984;149:496–500.
50. Montenegro R, Knuppel RA, Shah D, *et al.* The effect of serotonergic blockade in postpartum preeclamptic patients. *Am J Obstet Gynecol* 1985;153:130–3.
51. Hladunewich MA, Derby GC, Lafayette RA, *et al.* Effect of L-arginine therapy on the glomerular injury of preeclampsia: a randomized controlled trial. *Obstet Gynecol* 2006;107:886–95.
52. Liu Z, Wang XY, Yan NN. [Treatment of albuminuria in gestational hypertension puerpera in the severe preeclampsia stage by TCM therapy for stasis-removing and diuresis]. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2009;29:222–4.
53. Barrilleaux PS, Martin JN, Klauser CK, *et al.* Postpartum intravenous dexamethasone for severely preeclamptic patients without hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome: a randomized trial. *Obstet Gynecol* 2005;105:843–8.
54. Barrilleaux PS, Martin J, Klauser C, *et al.* Adjunctive intravenous dexamethasone in patients with severe preeclampsia not complicated by HELLP syndrome. *Am J Obstet Gynecol* 2003;189:S94.
55. Caughey AB. Editorial Comment: Does Immediate Postpartum Curettage of the Endometrium Accelerate Recovery From Preeclampsia–Eclampsia? A Randomized Controlled Trial. *Obstet Gynecol Surv* 2014;69:121–2.
56. HUNTER CA, Howard WF, McCORMICK CO. Amelioration of the hypertension of toxemia by postpartum curettage. *Am J Obstet Gynecol* 1961;81:884–9.
57. Gocmen A, Yayla M, Ceylan Erden A, *et al.* The effect of postpartum curettage in severe preeclampsia and eclampsia in recovery (Ağır preeklampsı ve eklampsı in iyileşmesinde postpartum kuretajın etkisi). *Perinatoloji Dergisi* 1996;4:24.
58. Salvatore CA, Carduz E, Ciccivizzo E, *et al.* [“Postpartum curettage in severe toxemia with and without premature loosening of the placenta”]. *Matern Infanc* 1967;26:275–86.
59. Magann EF, Martin JN, Isaacs JD, *et al.* Immediate postpartum curettage: accelerated recovery from severe preeclampsia. *Obstet Gynecol* 1993;81:502–6.
60. Magann EF, Bass JD, Chauhan SP, *et al.* Accelerated recovery from severe preeclampsia: uterine curettage versus nifedipine. *J Soc Gynecol Invest* 1994;1:210–4.
61. Gomez LM, De la Vega GA, Ludmir J, *et al.* Immediate postpartum curettage accelerates clinical recovery in severe preeclampsia. *Obstet Gynecol* 2005;105:111S.
62. Alkan A, Tugrul S, Oral O, *et al.* Effects of postpartum uterine curettage on maternal well-being in severe preeclamptic patients. *Clin Exp Obstet Gynecol* 2006;33:55–8.
63. Webster J, Koch HF. Aspects of tolerability of centrally acting antihypertensive drugs. *J Cardiovasc Pharmacol* 1996;27:S49–54.
64. Committee JF. *British National Formulary (BNF)*. 71st edn. BMJ Publishing Group Ltd and Royal Pharmaceutical Society, 2016.
65. Tan LK, de Swiet M. The management of postpartum hypertension. *BJOG* 2002;109:733–6.
66. Duley L, Gulmezoglu AM, Henderson-Smart DJ, *et al.* Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. *Cochrane Database Syst Rev* 2010;11.
67. Scherer RW, Langenberg P, von Elm E. Full publication of results initially presented in abstracts. *Cochrane Database Syst Rev* 2007;2:MR000005.
68. Khan K. The CROWN Initiative: journal editors invite researchers to develop core outcomes in women's health. *Br J Obstet Gynaecol* 2014;121:1181–2.
69. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2014;2.
70. National Institute for Health and Care Excellence. *NICE clinical guideline 127: hypertension in adults: diagnosis and management*, 2011.

Postpartum management of hypertensive disorders of pregnancy: a systematic review

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APPENDIX 2: Protocol for systematic review

**PROTOCOL: Management of hypertensive disorders of pregnancy in the postpartum
period: A systematic review**

Registration: PROSPERO CRD42015015527

http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015015527#.VL4ZI9KsWCK

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Amendments: Protocol first published 22/12/2014 (version 1.0). Protocol amended (version 2.0 25/03/2015) to include all reporting items from the PRISMA-P 2015 checklist, and PROSPERO registration number.

Review funder: NIHR Collaborations for Leadership in Applied Health Research and Care (funding A Cairns' fellowship)

Review sponsor: University of Oxford

Abstract

Rationale: Hypertensive disorders of pregnancy (gestational hypertension and pre-eclampsia) are a leading cause of direct maternal death in the UK, and affect approximately 5-10% of pregnancies. Hypertensive disorders of pregnancy persist during the postpartum period, and complications can occur during this time.

Research question: How should hypertensive disorders of pregnancy be managed in the postnatal period to minimise harm to patients and optimise quality of life?

Objectives:

1. Organisation of care: how should blood pressure be monitored in women with hypertensive disorders of pregnancy in the postnatal period?
2. What blood pressure thresholds should be used for anti-hypertensive treatment initiation, adjustment and cessation in the postnatal period?
3. Which anti-hypertensive medication(s) should be used in the postnatal period?
4. What are the benefits and harms of other therapeutic interventions for women with hypertensive disorders of pregnancy in the postnatal period?

Search strategy: Medline and nine other electronic databases will be searched for articles published from inception until October 2014 using a search strategy designed to capture all the relevant literature concerning the management of hypertensive disorders of pregnancy in the postnatal period.

Study eligibility criteria:

Population: postnatal women with gestational hypertension or pre-eclampsia as defined by study

Intervention: therapeutic intervention for hypertensive disorders of pregnancy

Comparisons: another intervention, placebo or no intervention

Study design: RCT, prospective or retrospective cohort study or case-control study

Publication date: no restrictions

Language: no restrictions

Data management and extraction: Two reviewers will first review the titles of articles yielded by the search, and then the abstracts of articles of potential relevance. The full papers of potentially eligible papers will be assessed, and data extracted independently by the two reviewers using a data extraction sheet. Differences in study selection and data extraction will be resolved by discussion.

Assessment of methodological quality: This will be done using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials, and for the assessment of bias in cohort and case-control studies we will use the Newcastle-Ottawa quality assessment scales.

Systematic review registration: This systematic review is registered with PROSPERO (International prospective register of systematic reviews).

Rationale***Definitions***

The National Institute for Health and Clinical Excellence (NICE) defines gestational hypertension as new-onset raised blood pressure ($\geq 140/90\text{mmHg}$) beyond 20 weeks gestation. NICE defines pre-eclampsia as new-onset raised blood pressure ($\geq 140/90\text{mmHg}$) together with new-onset significant proteinuria ($\geq 300\text{mg}/24\text{hr}$), beyond 20 weeks gestation (1).

The International Society for the Study of Hypertension in Pregnancy (ISSHP) defines pre-eclampsia as new-onset raised blood pressure (as defined by NICE) in association with one of new-onset significant proteinuria (as defined by NICE), maternal organ dysfunction or uteroplacental insufficiency (2).

Epidemiology

Hypertensive disorders of pregnancy remain the second commonest direct cause of maternal death in the USA.(3) Until recently this has also been the case in the UK (CMACE 2006-8)(4), but the most recent Confidential Enquiry into maternal deaths showed that for the triennium 2009-11, pre-eclampsia and eclampsia was the fourth commonest cause of direct death (behind thrombosis, genital tract sepsis and haemorrhage), with a rate of 0.42 deaths per 100,000 maternities (5).

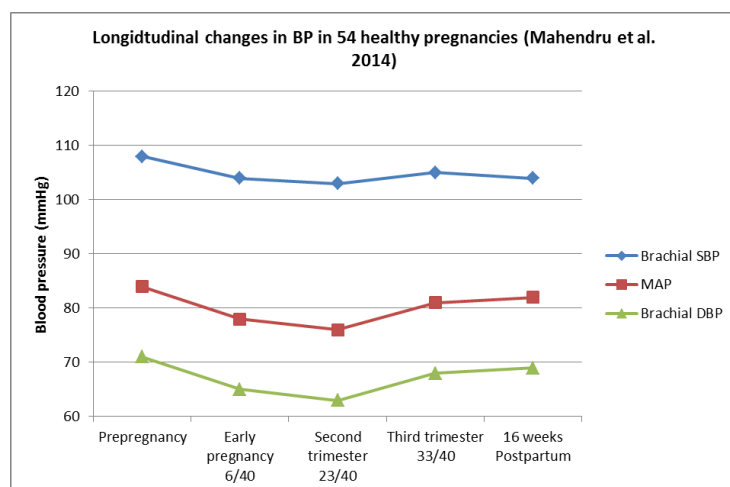
A recent population-based retrospective study in the United States found the rate of pre-eclampsia to be 3.4%. This study showed a slight, but significant increase, in the rates of both mild, and to a greater extent, severe pre-eclampsia over the period studied (1980-2010) (6).

Reviews of the literature, and national guidelines, quote rates of gestational hypertension between 6% (7) and 15% (8). A retrospective study using data from the National Hospital Discharge Survey in the United States (1987-2004) demonstrated an incidence of 30.6 cases of gestational hypertension per 1000 deliveries in 2003-2004 (3.1%) (9). In a well-designed large randomised controlled trial assessing preventative strategies for hypertensive disorders of pregnancy in low risk, nulliparous women the incidence of gestational hypertension across both groups was 6% (10).

Physiology of blood pressure in pregnancy and postpartum

As a result of a significant decrease in systemic vascular resistance (as early as 5 weeks gestation) (11), there is a decrease in arterial pressures from early in the first trimester. Arterial pressures reach a nadir in the second trimester, and then begin to rise in the third trimester, before reaching near-preconception levels in the postnatal period (12).

Figure 1: Serial blood pressures before, during and after pregnancy (reproduced from the data of Mahendru et al. 2014) (12)



In gestational hypertension and pre-eclampsia the normal pregnancy-induced vasodilatation is reversed. In untreated women with pre-eclampsia significant increases in systemic vascular resistance are seen and result in elevation of blood pressure (13).

Hypertensive disorders of pregnancy in the postpartum period

There has been considerable focus on blood pressure control during pregnancy, especially with respect to pregnancy outcome. However, it is recognised that hypertensive disorders of pregnancy do persist during the postpartum period, and that complications can occur during this time. A small retrospective observational study published in 1987 looked at 67 women with moderate-severe pre-eclampsia: there was often an initial decrease in blood pressure after delivery, but this was followed by a rise to hypertensive levels in many women. In 50% of cases the blood pressure was 150/100mmHg or higher on day 5 after birth. The authors recommended continuing blood pressure monitoring and treatment in the postpartum period for women with a diagnosis of pre-eclampsia (14).

Most women with hypertensive disorders of pregnancy will be treatment-free by 3 months postpartum. In women whose blood pressure normalised after delivery the mean time to normalisation in a retrospective cohort study of 62 women was 5.4 weeks (15). This rapidly changing blood pressure, with shifting medication requirement, poses an additional challenge in terms of how best to manage this down-titration.

Approximately one third of eclamptic seizures occur postpartum, and studies suggest that over half of these seizures occur more than 48 hours after birth. Chames et al. (2002) highlight the importance of education of women and clinicians regarding prodromal symptoms of eclampsia in the postnatal

period.⁽¹⁶⁾ A case series published in 2005 of patients who sustained a stroke in association with severe pre-eclampsia or eclampsia, showed that more than half (57%) of these strokes occurred in the postpartum period.⁽¹⁷⁾

Current guidelines

NICE guidelines highlight that very few clinical studies have addressed the management of blood pressure postpartum, and in practice clinical care is typically to continue antepartum antihypertensive medication and monitor blood pressure in the community with a focus on prevention of over-treatment.

NICE recommend frequency of monitoring in the postnatal period for both pre-eclampsia and gestational hypertension. The guidelines also stipulate thresholds for considering increasing or starting anti-hypertensive medication during this period (150/100 mmHg), and for reduction or stopping anti-hypertensive medication (consider at < 140/90 mmHg, and reduce at < 130/80 mmHg).⁽¹⁾

Research question

How should hypertensive disorders of pregnancy be managed in the postnatal period to minimise harm to patients and optimise quality of life?

Objectives

The aim is to establish what evidence exists to guide the optimal approach to management of gestational hypertension and pre-eclampsia in the postnatal period. We want to address the specific sub-questions:

1. Organisation of care: how should blood pressure be monitored in women with hypertensive disorders of pregnancy in the postnatal period?
2. What blood pressure thresholds should be used for anti-hypertensive treatment initiation, adjustment and cessation in the postnatal period?
3. Which anti-hypertensive medication(s) should be used in the postnatal period?
4. What are the benefits and harms of other therapeutic interventions for women with hypertensive disorders of pregnancy in the postnatal period?

Information sources and search strategy

The systematic review of 'management of hypertensive disorders of pregnancy in the postpartum period' will be conducted in line with the PRISMA statement.⁽¹⁸⁾ Completion of a systematic review

is an iterative process, and it may be that modifications to the original review protocol are required during its conduct.

A search strategy designed to capture all the relevant literature concerning the management of hypertensive disorders of pregnancy in the postnatal period will be developed by an experienced trial search co-ordinator. Potentially relevant studies will be identified following screening of title and abstract of studies captured by the search and full text assessed for suitability.

Resources to be searched from inception to October 2014:

- Medline (Appendix 3) and 9 other electronic databases
- Trial registers (ClinicalTrials.gov; Current Controlled Trials; WHO; PROSPERO)
- Meta Search Engines
- Hand searches of reference lists
- Citation searching on Scopus and Web of Science
- Related articles search on PubMed
- Contact with authors and professional bodies / organisations: Experts in this field will be contacted for their recommendations of potentially relevant citations(19)

Study eligibility criteria

INCLUSION CRITERIA

Population: postnatal women with hypertensive disorders of pregnancy (gestational hypertension or pre-eclampsia).

Intervention: therapeutic intervention for management of hypertensive disorders of pregnancy

Comparisons: other intervention, placebo or no intervention

Study design: randomised controlled trial, cohort study (prospective and retrospective) or case-control study; human studies only

Publication Date: no restrictions

Language: no restrictions

EXCLUSION CRITERIA

Exclude report / study if **any** exclusion criteria fulfilled:

Population: antenatal or intrapartum women with hypertensive disorders of pregnancy; end-organ complications of pre-eclampsia (eclampsia, renal failure, HELLP syndrome)

Intervention: treatment of HELLP syndrome (haemolysis, elevated liver enzymes and low platelets); prevention or management of eclampsia; prevention of postpartum hypertension; choice of anaesthetic or sedative in pre-eclampsia; observational studies

Comparisons: no control group

Study design: guidelines, reviews, expert opinions, letters, commentaries, audits, case series and case reports excluded; animal studies

Data extraction

Two reviewers (AC and LP) will screen the titles and abstracts of articles yielded by the search against the eligibility criteria. Discrepancies will be resolved by consensus before determining the list of full papers for review. The reports will be screened independently by the two reviewers, and discrepancies will be resolved by discussion before deciding which papers to include in the review.

Data from included studies will be extracted independently by the two reviewers using a piloted and standardised data extraction sheet. Differences in data extraction will be resolved by discussion.

In the event that there is more than one report published about a single study: the reports will be reviewed separately but the data from that study grouped in our analysis, and the primary reference will be used.

In the event that data is missing from a report (for example the sole publication is a conference abstract) we will contact the authors directly to request further detail.

The study characteristics (study size, population, setting, study design, methodology, intervention, controls if applicable, outcome measures, and follow up period) will be recorded and reported.

Data synthesis

The data extracted will be aggregate.

Due to the heterogeneous nature of the outcomes reported in these studies a narrative synthesis is planned.

For trials where the population study is peripartum (i.e. a mixture of antepartum, intrapartum and postpartum) we will extract the data for the postpartum women and analyse this. If this is not feasible from the reported data then we will contact the study authors to request the data for this subgroup.

Outcomes

The results of all clinically relevant outcomes in hypertensive disorders of pregnancy that would be important to clinicians and patients will be extracted and reported.

The main outcomes we are interested in are listed in table 1 below:

Table 1

	Outcome measures	Timing
Primary outcome(s)	Maternal mortality Major maternal morbidity (ischaemic stroke, intracranial haemorrhage, eclamptic seizure) Systolic blood pressure control Diastolic blood pressure control Mean arterial pressure control	Direct maternal deaths upto day 42 postpartum; later maternal deaths upto 1 year postpartum
Secondary outcome(s)	Critical care admission Postnatal readmission to secondary care Length of hospital stay following delivery Anti-hypertensive medication requirement Maternal side effects of intervention Development of pre-eclampsia with severe features Postnatal complication requiring intervention Urine output Laboratory values	

Assessment of methodological quality

We will assess the risk of bias in each study. For randomised trials this will be done using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials (Appendix 1, Table 2).(20) For each study the key domains will be identified, and then an overall assessment of bias within each trial made, according to the guidance published by the Cochrane Collaboration (Appendix 1, Table 2).

For the assessment of bias in cohort and case-control studies we will use the Newcastle-Ottawa quality assessment scales (Appendix 2, Tables 4 and 5).(21)

We will make a global assessment of bias across trials, based on the guidance from the Cochrane Collaboration (Appendix 1, Table 3):

- EITHER Most information is from trials at low risk of bias;
- OR most information is from trials at low or unclear risk of bias;
- OR the proportion of information from trials at high risk of bias is sufficient to affect the interpretation of results



Discussion

A Cochrane Review (2013) addresses the question of ‘prevention and treatment of postpartum hypertension’. This only includes randomised controlled trials (9 in total), and does not address the issue of monitoring blood pressure during this period.(22) Given the paucity of evidence cited in this area we believe there is a place for a review looking at all available evidence for the optimal approach to management of hypertensive disorders of pregnancy in the postpartum period.

Conflicts of interest

Neither AC nor LP have any conflicts of interest.

References

1. National Institute for Health and Care Excellence. NICE Clinical Guideline 107: Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. 2011.
2. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. *Pregnancy Hypertens.* 2014;4(2):97-104.
3. American College of Obstetricians and Gynecologists. Diagnosis and management of preeclampsia and eclampsia. ACOG Practice Bulletin. ACOG Practice Bulletin No. 33; 2002.
4. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG: An International Journal of Obstetrics & Gynaecology.* 2011;118 Suppl 1:1-203.
5. Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJ. Saving Lives, Improving Mothers' Care - Lessons learned to inform future maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-12.: Oxford: National Perinatal Epidemiology Unit, University of Oxford, MMBRACE-UK; 2014.
6. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. *BMJ.* 2013;347:f6564.
7. Yoder SR, Thornburg LL, Bisognano JD. Hypertension in pregnancy and women of childbearing age. *Am J Med.* 2009;122(10):890-5.
8. National Institute for Health and Care Excellence. NICE Clinical Guideline 107: Hypertension in pregnancy: Costing report. Implementing NICE guidance.; 2010.
9. Wallis AB, Saftlas AF, Hsia J, Atrash HK. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987-2004. *Am J Hypertens.* 2008;21(5):521-6.
10. Sibai BM, Caritis SN, Thom E, Klebanoff M, McNellis D, Rocco L, et al. Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med.* 1993;329(17):1213-8.
11. Chapman AB, Abraham WT, Zamudio S, Coffin C, Merouani A, Young D, et al. Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. *Kidney Int.* 1998;54(6):2056-63.
12. Mahendru AA, Everett TR, Wilkinson IB, Lees CC, McEniery CM. A longitudinal study of maternal cardiovascular function from preconception to the postpartum period. *J Hypertens.* 2014;32(4):849-56.
13. Visser W, Wallenburg HC. Central hemodynamic observations in untreated preeclamptic patients. *Hypertension.* 1991;17(6 Pt 2):1072-7.
14. Walters BN, Walters T. Hypertension in the puerperium. *Lancet.* 1987;2(8554):330.
15. Podymow T, August P. Postpartum course of gestational hypertension and preeclampsia. *Hypertens Pregnancy.* 2010;29(3):294-300.
16. Chames MC, Livingston JC, Ivester TS, Barton JR, Sibai BM. Late postpartum eclampsia: a preventable disease? *Am J Obstet Gynecol.* 2002;186(6):1174-7.
17. Martin JN, Jr., Thigpen BD, Moore RC, Rose CH, Cushman J, May W. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. *Obstet Gynecol.* 2005;105(2):246-54.
18. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097.

19. McManus RJ, Wilson S, Delaney BC, Fitzmaurice DA, Hyde CJ, Tobias RS, et al. Review of the usefulness of contacting other experts when conducting a literature search for systematic reviews. *BMJ*. 1998;317:1562-3.
20. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
21. Wells GA, Shea B, O'Connell D, J. P, V. W, M. L, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm].
22. Magee L, von Dadelszen P. Prevention and treatment of postpartum hypertension. *Cochrane Database Syst Rev*. 2013(4).

Appendix 1

Table 2: Cochrane Collaboration's tool for assessing risk of bias (*adapted from Higgins and Altman*)(20)

Bias domain	Source of bias	Support for judgment	Review authors' judgment (assess as low, unclear or high risk of bias)
Selection bias	Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and personnel*	Describe all measures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias	Blinding of outcome assessment*	Describe all measures used, if any, to blind outcome assessment from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition or exclusions where reported, and any re-inclusions in analyses for the review	Attrition bias due to amount, nature, or handling of incomplete outcome data
Reporting bias	Selective reporting	State how selective outcome reporting was examined and what	Reporting bias due to selective

		was found	outcome reporting
Other bias	Anything else, ideally Pre-specified	State any important concerns about bias not covered in the other domains in the tool	Bias due to problems not covered elsewhere

*Assessments should be made for each main outcome or class of outcomes.

Table 3: Approach to formulating summary assessments of risk of bias for each important outcome (across domains) within and across trials (*adapted from Higgins and Altman*)(20)

Risk of bias	Interpretation	Within a trial	Across trials
Low risk of bias	Bias, if present, is unlikely to alter the results seriously	Low risk of bias for all key domains	Most information is from trials at low risk of bias
Unclear risk of bias	A risk of bias that raises some doubt about the results	Low or unclear risk of bias for all key domains	Most information is from trials at low or unclear risk of bias
High risk of bias	Bias may alter the results seriously	High risk of bias for one or more key domains	The proportion of information from trials at high risk of bias is sufficient to affect the interpretation of results

Appendix 2

Table 4: Newcastle-Ottawa quality assessment scale case control studies(21)

A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection	Is the case definition adequate?	a) Yes, with independent validation ★ b) Yes, e.g. record linkage or based on self-reports c) No description
	Representativeness of the cases	a) Consecutive or obviously representative series of cases ★ b) Potential for selection biases not stated
	Selection of controls	a) Community controls ★ b) Hospital controls c) No description
	Definition of controls	a) No history of disease (endpoint) ★ b) No description of source
Comparability	Comparability of cases and controls on the basis of the design or analysis	a) Study controls for <<_>> (select the post important factor) ★ b) Study controls for any additional factor ★
Exposure	Ascertainment of exposure	a) Secure records (e.g. surgical records) ★ b) Structured interview where blind to case/control status ★ c) Interview not blinded to case/control status d) Written self-report or medical record only e) No description
	Same method of ascertainment for cases and controls	a) Yes ★ b) No
	Non-response rate	a) Same rate for both groups ★ b) Non-respondents described c) Rate different and no designation

Table 5: Newcastle-Ottawa quality assessment scale cohort studies(21)

A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection	Representativeness of the exposed cohort	a) Truly representative of the average <<_>> (describe) in the community ★ b) Somewhat representative of the average <<_>> (describe) in the community ☐ c) Selected group of users e.g. nurses, volunteers d) No description of the derivation of the cohort
	Selection of the non-exposed cohort	a) Drawn from the same community as the exposed cohort ★ b) Drawn from a different source c) No description of the derivation of the non-exposed cohort
	Ascertainment of exposure	a) Secure record (e.g. surgical records) ★ b) Structured interview ★ c) Written self-report d) No description
	Demonstration that the outcome of interest was not present at start of study	a) Yes ★ b) No
Comparability	Comparability of cases and controls on the basis of the design or analysis	a) Study controls for <<_>> (select the post important factor) ★ b) Study controls for any additional factor ★
Outcome	Assessment of outcome	a) Independent blind assessment ★ b) Record linkage ★ c) Self-report d) No description
	Was follow-up long enough for outcomes to occur	a) Yes (select an adequate follow up period for outcome of interest) ★ b) No
	Adequacy of follow-up of cohorts	a) Complete follow-up – all subjects accounted for ★ b) Subjects lost to follow-up unlikely to introduce bias: >_ _ % (select an adequate %) follow-up rate, or description provided of those lost) ★ c) Follow-up rate < _ _ % (select an adequate %) and no description of those lost d) No statement

Appendix 3: Medline search strategy

# ▼	Searches	Results
1	Pregnancy/ and Hypertension/	9226
2	exp Hypertension, Pregnancy-Induced/	29022
3	((pregnan* or gestation* or maternal or prenatal or pre-natal or antenatal or ante-natal or antepart* or ante-part* or obstetric*) and (hypertens* or blood pressure or bp or dbp or sbp or diastolic or systolic)).ti.	6787
4	((pregnan* or gestation* or maternal or prenatal or pre-natal or antenatal or ante-natal or antepart* or ante-part* or obstetric*) adj3 (hypertens* or blood pressure or bp or dbp or sbp or diastolic or systolic)).ti,ab.	12434
5	(eclamp* or preeclamp* or pre-eclamp* or hellp).ti,ab.	25194
6	1 or 2 or 3 or 4 or 5	46611
7	Postnatal Care/	4044
8	Aftercare/	6684
9	Postpartum Period/ and Maternal Health Services/	126
10	exp Puerperal Disorders/ and Maternal Health Services/	196
11	Postpartum period/ and (exp Antihypertensive agents/ or exp calcium channel blockers/ or exp Angiotensin-Converting Enzyme Inhibitors/ or exp Adrenergic beta-Antagonists/ or exp Diuretics/)	187
12	exp Puerperal disorders/ and (exp Antihypertensive agents/ or exp calcium channel blockers/ or exp Angiotensin-Converting Enzyme Inhibitors/ or exp Adrenergic beta-Antagonists/ or exp Diuretics/)	237
13	Postpartum period/ and exp Curettage/	30
14	exp Puerperal disorders/ and exp Curettage/	118
15	Postpartum period/ and hypertension/dt, th	33
16	exp Puerperal disorders/ and hypertension/dt, th	54
17	exp Puerperal disorders/dt, th	6408
18	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 (care or healthcare or service* or program* or scheme* or intervention*)).ti,ab.	4407
19	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 (clinic? or unit? or visit* or referral? or appointment?)).ti,ab.	1491
20	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 (manage* or treat* or therap* or medication? or recovery)).ti,ab.	7287
21	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 (antihypertens* or anti-hypertens* or calcium channel block* or beta block* or b block* or ace inhibitor* or angiotensin converting enzyme inhibitor* or diuretic*)).ti,ab.	41
22	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 (evaluat* or assess* or screen* or diagnos* or monitor* or follow up or supervis*)).ti,ab.	7562
23	((postnatal or post-natal or postpart* or post-part* or puerper*) adj5 curet*).ti,ab.	82
24	(postnatal or post-natal or postpart* or post-part* or puerper*).ti.	41491
25	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	64775

26	6 and 25	1896
27	((postnatal or post-natal or postpart* or post-part* or puerper*) and (hypertens* or blood pressure)).ti.	270
28	26 or 27	1990
29	exp animals/ not humans.sh.	4079856
30	(rat or rats or rodent? or mice or mouse or cow or cows or cattle or calf or calves or ewe? or sheep or goat or ruminant? or pig or pigs or minipig? or chicken? or horse or horses or murine or bovine or ovine or porcine or animal?).ti.	1682619
31	29 or 30	4373527
32	28 not 31	1881



Appendix 3: Systematic review PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7; Table 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7 (narrative)



Appendix 3: Systematic review PRISMA 2009 checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7; Appendix S4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7-8; Appendix S6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-13; Tables 2a+b; Appendix S5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-8; Appendix S6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: www.prisma-statement.org.

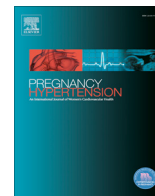
APPENDIX 4: Publication of survey

Cairns AE, Tucker KL, Leeson P, Mackillop L, McManus RJ. Survey of healthcare professionals regarding adjustment of antihypertensive medication(s) in the postnatal period in women with hypertensive disorders of pregnancy. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health*. 2016;6(4):256-8.



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journal homepage: www.elsevier.com/locate/preghy

Short communication

Survey of healthcare professionals regarding adjustment of antihypertensive medication(s) in the postnatal period in women with hypertensive disorders of pregnancy

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ABSTRACT

Hypertensive disorders of pregnancy affect approximately one in ten pregnancies and often persist postpartum. Their postnatal course can be unpredictable and complications may occur, hence control remains important but is informed by little evidence. Clinicians from UK primary and secondary healthcare were invited to complete a survey regarding antihypertensive adjustment postpartum. The response rate was 101/390 (26%). Labetalol was the commonest antihypertensive used. Most participants reported following national guidelines when reducing, although not increasing, antihypertensive medications. The results suggest an unwarranted and unjustifiable variation in management – underlining the evidence gap – additional research is needed to inform the standardisation of care.

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1. Introduction

There is no international consensus regarding the diagnostic criteria for hypertensive disorders of pregnancy. The National Institute for Health and Care Excellence (NICE) defines gestational hypertension as new-onset hypertension ($\geq 140/90$ mmHg) developing after 20 weeks gestation, and pre-eclampsia as new-onset hypertension with significant proteinuria [1]. Gestational hypertension affects 6% [2,3] – 15% [4] of pregnancies, with pre-eclampsia affecting around 3% [5]. Hypertensive disorders of pregnancy remain a leading direct cause of maternal death in the UK, USA and worldwide [6–8].

Research to date has largely focussed on blood pressure (BP) management during pregnancy: a Cochrane review highlighted a paucity of evidence underpinning BP control postpartum despite recognition that hypertensive disorders of pregnancy (and complications thereof) can persist following delivery [9]. Approximately 30% of eclampsia occurs after birth, and 14–50% of these seizures happen beyond 48 hours [10–12]. A case series showed that 57% of strokes, sustained in association with severe pre-eclampsia,

occurred postpartum [13]. A further retrospective cohort study found a post-discharge postpartum acute cerebrovascular event rate of 14.8/100,000 births [14].

Despite this, most women with hypertensive disorders of pregnancy will be treatment-free by three months postpartum [15], so managing down-titration of antihypertensive medication during this time of potentially rapidly changing BP is a real issue. National and international guidance provides largely expert-derived thresholds for medication adjustment with little detail concerning, for example, dose reduction (frequency and amount), or management of multiple medications [1]. We surveyed healthcare professionals with experience of managing gestational hypertension seeking their views regarding the adjustment of antihypertensive medication in postnatal women with hypertensive disorders of pregnancy and mapped the variation in clinical practice.

2. Methods

The study received ethical approval from the University of Oxford (MS-IDREC-C1-2015-019).

We conducted an online survey of prescribing and non-prescribing clinicians, in primary and secondary care, in Berkshire, Buckinghamshire, Northamptonshire and Oxfordshire. This study

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Table 1

Summary of invitations and responses for survey.

	Invitations sent out	Responses
GPs	139	40 (29%) ^a
Obstetricians	123	41 (33%)
Midwives	128	20 (16%)
TOTAL	390	101 (26%)

^a 5 further responders, but no details completed.

did not involve any patient data, and no identifiable or confidential data about participants were recorded, simply job role, place of work and age.

We planned to invite 300 clinicians to participate (200 prescribers, 100 non-prescribers), aiming for a 50% response rate (150 responses). Participants were invited to complete the questionnaire by email from February to June 2015. The email contained a link to the online survey and the participant information sheet was attached. Reminder emails were sent after three weeks. The primary outcome was clinicians' preference for which antihypertensive to use postpartum. Two questions were asked to elucidate this: Participants were asked to list all the antihypertensive medications they would consider using postpartum and then to choose which of these they used most commonly.

3. Results

Invitations were sent to 262 prescribing clinicians (obstetricians and general practitioners), and 128 non-prescribers (hospital and community midwives). Overall the response rate was 101/390 (26%): 81/262 (31%) prescribers and 20/128 (16%) non-prescribers (Table 1). In our analysis we have adjusted the denominators according to the number of participants who answered each question.

Labetalol was by far the most frequently used antihypertensive, with 89/98 (91%) stating that they would use it postpartum, 83/98 (85%) as their most common choice (Fig. 1).

We asked clinicians to select the highest BP thresholds at which they would consider reducing the dose of antihypertensive. 59/94

(63%) selected a systolic BP (SBP), and 74/94 (79%) a diastolic BP (DBP) in line with NICE guidance (130–140/80–90 mmHg). Midwives selected lower thresholds than prescribing clinicians: 12/16 (75%) selected a SBP of 110–120 mmHg, 10/16 (63%) a DBP of 60–70 mmHg. We asked participants to select the lowest BP thresholds at which they would increase the dose of antihypertensive. Fewer participants responded in line with NICE guidance: 43/94 (46%) selected 150 mmHg SBP and 33/94 (35%) selected 100 mmHg DBP. In this case more GPs selected lower thresholds than did obstetricians.

We asked prescribing clinicians to state how they would approach dose reduction of an antihypertensive in response to low BP. A diverse range of responses was given: most commonly that it would depend on the BP [25/78 (32%)] or be based on the prescribing formulary [19/78 (24%)]. Responses were heterogeneous regardless of respondents' specialty. We asked all clinicians about how down-titration of multiple medications should be approached. Again the responses varied although 43/94 (46%) stated that they would reduce one medication at a time.

4. Discussion

Overall this small survey suggested considerable heterogeneity in current management of hypertension postpartum. This may reflect the lack of evidence and guidance in this area: where guidance does exist, for example regarding selection of antihypertensive (labetalol as first line) or BP thresholds for medication adjustment, there was greater consistency in response, albeit, in the case of up-titration, more from obstetricians than GPs. This may be reflective of obstetricians' familiarity with using the same threshold for medication commencement or increase during pregnancy. However, as no guidance exists regarding how to reduce doses when down-titrating, or how to adjust multiple medications, it is perhaps not surprising that there were a wide range of responses from all groups. Such diversity may result in patients receiving different advice from different healthcare professionals, with potentially negative consequences for continuity of care. It may also result in differing standards of care across different NHS settings.

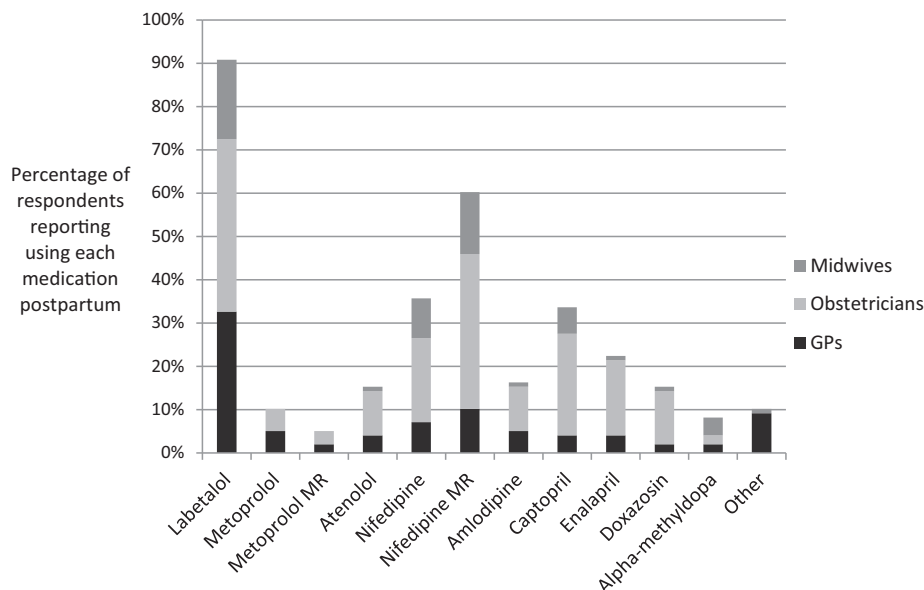


Fig. 1. Postpartum medication selection. (9 GPs commented they would not commence a new agent, but would continue the medication started by the patient's obstetric team. 2 GPs commented they rarely encountered this problem. 1 GP stated they would continue what the patient had been taking during pregnancy. 1 midwife selected labetalol and also 'other' commenting she had not worked in the postnatal area for 12 years.)

One strength of this survey was the broad spectrum of health-care professionals surveyed, across a range of different settings, including both district general and teaching hospitals, urban and rural primary care centres. Its limitations were the low response rate (Table 1), and the relatively small number of responses (101 individuals). This might bias the results towards the opinions of clinicians with more interest or expertise in this area, rather than obtaining a true cross-sectional view.

Nevertheless, this survey supports the need for additional research about how to manage women with hypertension postpartum in order to optimise BP control and improve patient experience. Research is needed to formulate uniform approaches to BP monitoring and medication down-titration, and to streamline handover from secondary to primary care. One potential solution – effective in essential hypertension – could be BP self-management, using validated home BP monitors and a standardised algorithm for medication adjustment [16].

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Authors' contributions

AC, KT, LM, PL and RM all contributed to the study design. AC undertook the data collection and analysis. AC, KT, LM, PL and RM all contributed to the preparation of this manuscript and have seen and approved the final version.

Conflicts of interest

None declared.

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References

- [1] National Institute for Health and Care Excellence, NICE Clinical Guideline 107: Hypertension in pregnancy: the management of hypertensive disorders during pregnancy, 2011.
- [2] S.R. Yoder, L.L. Thornburg, J.D. Bisognano, Hypertension in pregnancy and women of childbearing age, *Am. J. Med.* 122 (10) (2009) 890–895.
- [3] B.M. Sibai, S.N. Caritis, E. Thom, M. Klebanoff, D. McNellis, L. Rocco, R.H. Paul, R. Romero, F. Witter, M. Rosen, et al., Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units, *N. Engl. J. Med.* 329 (17) (1993) 1213–1218.
- [4] National Institute for Health and Care Excellence, NICE Clinical Guideline 107: Hypertension in pregnancy: Costing report. Implementing NICE guidance, 2010.
- [5] C.V. Ananth, K.M. Keyes, R.J. Wapner, Pre-eclampsia rates in the United States, 1980–2010: age-period-cohort analysis, *BMJ* 347 (2013) f6564.
- [6] M. Knight, D. Tuffnell, S. Kenyon, J. Shakespeare, R. Gray, J.J. Kurinczuk, Saving Lives, Improving Mothers' Care-Surveillance of maternal deaths in the UK 2011–13 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–13, Oxford: National Perinatal Epidemiology Unit, University of Oxford, 2015.
- [7] American College of Obstetricians and Gynecologists, Diagnosis and management of preeclampsia and eclampsia, ACOG Practice Bulletin No. 33, 2002.
- [8] K.S. Khan, D. Wojdyla, L. Say, A.M. Gulmezoglu, P.F. Van Look, WHO analysis of causes of maternal death: a systematic review, *Lancet* 367 (9516) (2006) 1066–1074.
- [9] L. Magee, P. von Dadelszen, Prevention and treatment of postpartum hypertension, *Cochrane Database Syst. Rev.* 4 (2013) CD004351.
- [10] M.C. Chames, J.C. Livingston, T.S. Ivester, J.R. Barton, B.M. Sibai, Late postpartum eclampsia: a preventable disease?, *Am. J. Obstet. Gynecol.* 186 (6) (2002) 1174–1177.
- [11] G. Kayem, J.J. Kurinczuk, P. Spark, P. Brocklehurst, M. Knight, U.K.O.S. System, Maternal and obstetric factors associated with delayed postpartum eclampsia: a national study population, *Acta Obstet. Gynecol. Scand.* 90 (9) (2011) 1017–1023.
- [12] D.L. Watson, B.M. Sibai, D.C. Shaver, J.V. Dacus, G.D. Anderson, Late postpartum eclampsia: an update, *South. Med. J.* 76 (12) (1983) 1487–1489.
- [13] J.N. Martin Jr., B.D. Thigpen, R.C. Moore, C.H. Rose, J. Cushman, W. May, Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure, *Obstet. Gynecol.* 105 (2) (2005) 246–254.
- [14] D.A. Hovsepian, N. Sriram, H. Kamel, M.E. Fink, B.B. Navi, Acute cerebrovascular disease occurring after hospital discharge for labor and delivery, *Stroke* 45 (7) (2014) 1947–1950.
- [15] T. Podymow, P. August, Postpartum course of gestational hypertension and preeclampsia, *Hypertension Pregnancy* 29 (3) (2010) 294–300.
- [16] R.J. McManus, J. Mant, E.P. Bray, R. Holder, M.I. Jones, S. Greenfield, B. Kaambwa, M. Banting, S. Bryan, P. Little, B. Williams, F.D. Hobbs, Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial, *Lancet* 376 (9736) (2010) 163–172.

APPENDIX 5: Audit tool

GESTATIONAL HYPERTENSION	
	Date of delivery: Gestation at delivery: Mode of delivery: Birthweight: Gestational HTN / Pre-eclampsia Medication: yes / no Duration of PN stay: (Duration of PN stay until d/c to MLC:)
Medication on discharge Medication increases after d/c	
GP DETAILS:	
MONITORING	
Day 1	
Day 2	
Once between D3 - 5	
As indicated if Tx changed	
TREATMENT	
Continue AN Tx	
Switch aMD within 2/7 of delivery	
Commence Tx if BP $\geq$ 150/100	
Reduce Tx if BP < 130/80	
CARE PLANS	
Who will provide F/U	
Frequency of BP monitoring	
Thresholds for Tx adjustment	
Indications for referral for BP r/v	
FOLLOW-UP	
Medical review 2/52 PN	
Medical review 6-8/52 PN	
If still requiring Tx 6-8/52 PN offer specialist referral	
Duration of medication	
PN readmission for BP control	

PRE-ECLAMPSIA	
	Date of delivery: Gestation at delivery: Mode of delivery: Birthweight: Gestational HTN / Pre-eclampsia Medication: yes / no Duration of PN stay: (Duration of PN stay until d/c to MLC:)
Medication on discharge Medication increases after d/c	
GP DETAILS:	
MONITORING	
QDS whilst inpatient	
Asked about headaches/epigastric pain when BP measured	
<i>Not medicated</i>	
Once between D3 - 5	
If BP abnormal D3-5: on alternate days until normal	
<i>Medicated</i>	
Every 1-2d for up to 2/52 until BP normal and off Tx	
TREATMENT	
Continue AN Tx	
Switch aMD within 2/7 of delivery	
Commence Tx if BP $\geq$ 150/100	
Reduce Tx if BP < 130/80	
CARE PLANS	
Who will provide F/U	
Frequency of BP monitoring	
Thresholds for Tx adjustment	
Indications for referral for BP r/v	
Advice re: self-monitoring of Sx	
FOLLOW-UP	
Medical review 2/52 PN	
Medical review 6-8/52 PN	
If still requiring Tx 6-8/52 PN offer specialist referral	
Duration of medication	
PN readmission for BP control	



APPENDIX 6: GP Questionnaire for Audit

Silver Star Unit
Level 6, Women's Centre
John Radcliffe Hospital
Headley Way
Oxford
OX3 9DU
FAX: 01865 228998

30th May 2014

Dear Dr

We are currently auditing the postnatal care of ladies who have developed raised blood pressure in pregnancy, in order to improve our standards of care, in line with NICE guidance, and patient satisfaction. We recognise that a crucial part of this process is to improve our communication with Primary Care following delivery. Therefore I would be very grateful if you would take the time to complete the short enclosed questionnaire regarding the following patient. Please be assured that all data is being processed and stored anonymously (the number in the top right hand corner is the record number by which we identify patients).

Name:

DOB:/...../.....

Date of delivery:/...../.....

Please could you fax the questionnaire to the number above? Many thanks for your assistance. If you have any questions please do not hesitate to contact me.

Kind regards,

Dr Alexandra Cairns

Registrar in Obstetrics and Gynaecology, Bleep 1062



1) Were there any medication increases after discharge? YES / NO

If yes, what?

2) What was the total duration of anti-hypertensive Tx? What date was it stopped?

3) What thresholds did you use to adjust treatment?
i.e. if $< 130/80$ was it reduced, if $\geq 150/100$ was it increased

4) Did you receive any sort of care plan for after discharge? YES / NO

If yes, details of who will provide follow up?

If yes, thresholds for treatment adjustment?

If yes, indications for referral for BP review?

5) Did they have a review at 2/52 postnatal? YES / NO

6a) Did they have a review at 6-8/52 postnatal? YES / NO

6b) If still hypertensive at 6-8 week check were they offered specialist referral?
YES / NO / NA

7) Are you aware of any PN readmission for BP control? YES / NO

APPENDIX 7: Survey protocol

Study Title: Survey of healthcare professionals regarding adjustment of anti-hypertensive medication(s) in the postnatal period in women with hypertensive disorders of pregnancy

Short title: Postnatal anti-hypertensive medication adjustment survey

Med IDREC Ref: MS-IDREC-C1-2015-019

Date and Version No: 23/12/2014 V1.0

Chief Investigator: Dr Alexandra Cairns, Nuffield Department of Primary Care Health Sciences, University of Oxford
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Sponsor: University of Oxford

Funder: National Institute for Health Research (NIHR)

Chief Investigator Signature: 

No conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the authorised individuals from the University of Oxford, the Investigator Team and members of the Medical Sciences Interdisciplinary Research Ethics Committee (Medical Sciences IDREC), unless authorised to do so.

Abstract

Background

Gestational hypertension, defined as new onset blood pressure (BP) of $\geq 140/90$ mmHg after 20 weeks gestation, affects between 6 and 15% of pregnancies. There has been considerable focus on blood pressure control during pregnancy, especially with respect to pregnancy outcome. However, it is recognised that hypertensive disorders of pregnancy do persist during the postpartum period, and that complications can occur during this time. We are setting up a randomised trial development pilot study to assess the feasibility of self-management of antihypertensive medication postpartum. Participants in the intervention group will be provided with a validated home blood pressure monitor to use daily, in conjunction with an individualised medication adjustment schedule.

The paucity of evidence regarding adjustment of anti-hypertensive medications in the postnatal period is one of the challenges to the implementation of self-management approaches in this cohort. In order to help guide us in creating general principles on which to base these medication adjustment schedules we plan to survey healthcare professionals involved in the care of postnatal women with hypertensive disorders of pregnancy about their usual practices. This will include Obstetricians, Obstetric Physicians, General Practitioners, Midwives and Health Visitors.

Research questions

Do clinicians have a preference for a particular anti-hypertensive medication for use in the postnatal period; what blood pressure thresholds do clinicians use when increasing or decreasing anti-hypertensive medications in the postnatal period; when down-titrating anti-hypertensive medications, do clinicians reduce the dose by a certain proportion at a time; when down-titrating multiple anti-hypertensive medications how do clinicians approach this; do the approaches used differ between different clinical groups?

Methodology

We are planning to conduct a service evaluation study in several primary and secondary care centres. This will involve the use of online questionnaires. We have designed two separate questionnaires: one for prescribing healthcare professionals; one for non-prescribing healthcare professionals. The survey will be completed anonymously. Participants will be invited to complete the questionnaire via email. We will record the number of healthcare professionals whom we ask to complete each survey in order to calculate a response rate. We are aiming to survey 200 prescribing clinicians and 100 non-prescribers.

Outcome measures

Response rate; demographics of respondents

Prescribing healthcare professionals: Preference of anti-hypertensive medication postpartum; blood pressure thresholds used for medication reduction/increase; proportion by which medication dose reduced when down-titration; approach to down-titrating multiple medications

Non-prescribing healthcare professionals: What anti-hypertensive medications they have experience of patients taking postpartum; what blood pressure thresholds would they use to refer a patient to a prescribing clinician for consideration of medication reduction/increase and how these would affect the urgency of such a change; when a patient is on multiple medications, what is their view about how this down-titration should be approached.

Synopsis

Study Title	Survey of healthcare professionals regarding adjustment of anti-hypertensive medication(s) in the postnatal period in women with hypertensive disorders of pregnancy	
Short Title	Postnatal anti-hypertensive medication adjustment survey	
Study Design	Service evaluation online survey	
Study Participants	Healthcare professionals involved in the care of postnatal women with medicated hypertensive disorders of pregnancy	
Planned Sample Size	200 prescribers + 100 non-prescribers	
Planned Study Period	3 months (01/02/2015 – 01/05/2015)	
	Objectives	Outcome Measures
Primary	Do clinicians have a preference for a particular anti-hypertensive medication for use in the postnatal period	Frequency of use of each anti-hypertensive medication Which anti-hypertensive medication(s) do clinicians state they use 'most commonly'
Secondary	What blood pressure thresholds do clinicians use when increasing or decreasing anti-hypertensive medications in the postnatal period	Blood pressure thresholds used for medication reduction Blood pressure thresholds used for medication increase
	When down-titrating anti-hypertensive medications, do clinicians reduce the dose by a certain proportion at a time	Proportion by which medication dose reduced when down-titrating
	When down-titrating multiple anti-hypertensive medications how do clinicians approach this	Approach to down-titrating multiple medications
	Do the approaches used differ between different clinical groups	Comparison between different groups
	Survey response rate	Number of completed surveys / number of healthcare professionals invited to complete survey

Abbreviations

BP	Blood Pressure
CI	Chief Investigator
CMACE	Centre for Maternal And Child Enquiries
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
GP	General Practitioner

HDP	Hypertensive Disorders of Pregnancy
ICF	Informed Consent Form
IDREC	Interdisciplinary Research Ethics Committee
NHS	National Health Service
NICE	National Institute for health and Care Excellence
NIHR	National Institute for Health Research
PIS	Participant Information Sheet
SOP	Standard Operating Procedure
ST	Specialty Trainee
SST	Sub-Specialty Trainee

Background

Gestational hypertension, defined as new-onset blood pressure (BP) of $\geq 140/90$ mmHg after 20 weeks gestation, affects between 6 and 15% of pregnancies. A recent population-based retrospective study in the USA found the rate of pre-eclampsia (blood pressure $\geq 140/90$ mmHg and new onset significant proteinuria ≥ 300 mg/24hr) to be 3.4% (1). Hypertensive disorders of pregnancy remain the second commonest direct cause of maternal death in the UK (CMACE 2006-8) (2) and the USA (3).

There has been considerable focus, both within research groups and from the NICE guidance, on blood pressure control during pregnancy, especially with respect to pregnancy outcome. However, it is recognised that hypertensive disorders of pregnancy do persist during the postpartum period, and that complications can occur during this time. Most women with hypertensive disorders of pregnancy will be treatment-free by 3 months postpartum. In women whose blood pressure normalised after delivery the mean time to normalisation in a retrospective cohort study of 62 women was 5.4 weeks (4). This rapidly changing blood pressure, with shifting medication requirement, poses an additional challenge in terms of how to manage the down-titration of antihypertensive medications in this period. There is little firm evidence regarding the best way in which to approach this medication adjustment: NICE recommends thresholds at which to consider dose reduction or increase, but does not comment about how much to reduce a dose by, the frequency of dose reduction, or how to approach the management of multiple medications (5).

Previous work in the non-pregnant population has shown that self-monitoring and self-titration of anti-hypertensive medications in essential hypertension is both feasible and more effective than usual care. The TASMINH2 randomised controlled trial (2010) demonstrated that self-management of blood pressure in patients with poorly controlled essential hypertension resulted in a statistically significant reduction in mean systolic blood pressure compared with patients undergoing usual care (difference between groups at 12 months 5.4mmHg, $p=0.0004$) (6). Women with medicated hypertensive disorders of pregnancy would seem to be an ideal cohort in whom to apply these experiences: the disease has, in general, a limited time course meaning that intensive monitoring is more reasonable and more likely to be adhered to. Pregnant women are by definition in a younger age group than the majority of those with essential hypertension, and may be more comfortable with the use of technology to assist in disease monitoring. Women might also be more empowered

in the setting of a recent pregnancy to take greater responsibility for their health. The American Society of Hypertension states that 'home blood pressure monitoring is theoretically ideal for monitoring changes in blood pressure during pregnancy', but notes that 'the extent to which it will improve the evaluation and management of hypertension during pregnancy has yet to be shown' (7). If self-management in the postpartum period proves to be a feasible, acceptable and a successful strategy for management of blood pressure, it could lead to a reduction in the length of inpatient stay, readmissions and the number of postpartum visits, with cost-saving implications for both primary and secondary care.

We are setting up a randomised trial development pilot study (SNAP-HT) to assess the feasibility of self-management of antihypertensive medication versus usual care in hypertensive disorders of pregnancy postpartum. Women randomised to self-management of blood pressure will be provided with, and taught to use, a validated home blood pressure monitor, and perform daily blood pressure readings until they have discontinued treatment. Participants will be provided with an individualised medication adjustment schedule based on: their current treatment (which drugs, what doses); NICE guidance for management of hypertension in pregnancy (5). The individualised medication adjustment schedules for each participant will be created by the research team in conjunction with the participant's usual care team.

The paucity of evidence regarding adjustment of anti-hypertensive medications in the postnatal period is one of the challenges to implementation of self-management approaches. In order to help guide us in creating general principles on which to base these medication adjustment schedules we wish to survey healthcare professionals involved in the care of postnatal women with hypertensive disorders of pregnancy about their usual practices. This will include Obstetricians, Obstetric Physicians, General Practitioners, Midwives and Health Visitors.

If we fail to demonstrate any uniformity in usual practice we will then utilise the clinical experience within our research team (which includes an obstetrician, an obstetric physician, a hypertension specialist, general practitioners and midwives) in conjunction with advice from a clinical pharmacologist to construct general principles for down-titration.

Research questions

1. Do clinicians have a preference for a particular anti-hypertensive medication for use in the postnatal period?
2. What blood pressure thresholds do clinicians use when increasing or decreasing anti-hypertensive medications in the postnatal period?
3. When down-titrating anti-hypertensive medications, do clinicians reduce the dose by a certain proportion at a time?
4. When down-titrating multiple anti-hypertensive medications how do clinicians approach this?
5. Do the approaches used differ between different clinical groups?

Outcome measures

Prescribing healthcare professionals

- Response rate
- Demographics of respondents (job role, age, geographical region)

- Preference of anti-hypertensive medication postpartum
 - Frequency of use of each anti-hypertensive medication
 - Which anti-hypertensive medication(s) do clinicians state they use 'most commonly'
- Blood pressure thresholds used for medication reduction
- Blood pressure thresholds used for medication increase
- Proportion by which medication dose reduced when down-titrating
- Approach to down-titrating multiple medications

Non-prescribing healthcare professionals

- Response rate
- Demographics of respondents (job role, age, geographical region)
- Which anti-hypertensive medications they have experience of patients taking postpartum
- What blood pressure threshold would they use to refer a patient to a prescribing clinician for consideration of medication reduction
- What blood pressure threshold would they use to refer a patient to a prescribing clinician for consideration of medication increase
- When a patient is on multiple medications what is their view about how this down-titration should be approached

Study population

Healthcare professionals involved in the care of postnatal women with hypertensive disorders of pregnancy about their usual practices.

Included:

Obstetricians: Consultants, ST3-7 and SST, Associate Specialists, Staff Grades
Obstetric Physicians: Consultants, Registrars
General Practitioners and GP Registrars
Midwives
Health Visitors

Excluded:

Foundation doctors
GP VTS ½
Obstetrics and Gynaecology ST1/2
Medical students
Student midwives
Student nurses

Study design

We are planning to conduct a service evaluation study in several NHS primary and secondary care centres (Oxford University Hospitals NHS Trust, Royal Berkshire Hospitals NHS Foundation Trust, Northampton General Hospital NHS Trust, Buckinghamshire Healthcare NHS Trust, NIHR Clinical Research Network: Thames Valley and South Midlands).

This will involve the use of online questionnaires. We have designed two separate questionnaires: one for prescribing healthcare professionals (Appendix 1); one for non-prescribing healthcare professionals (Appendix 2). These have been designed to answer the research questions as defined

above. This study will not involve the use of any patient data, and no identifiable or confidential data about participants will be recorded. The survey will be completed anonymously. No randomisation will take place, and there will be no alteration of patient care.

Study procedures

Participants will be invited to complete the questionnaire via email. This email will contain a link to the appropriate survey (SurveyMonkey). Participants will have one month to respond to the invitation to complete the questionnaire. A reminder email will be sent 1 week before the closing date. A participant information sheet will be attached to the invitation email.

The first page of the survey will contain the informed consent statements, to which participants will have to agree before they can begin completion of the survey.

Demographic data about respondents will be collected as follows: job role, country and unit of work, age. The surveys will have a multiple choice structure, with space for free text 'other' responses. All questions require a response.

Participants will be free to withdraw from the survey at any stage prior to completion. Data from incomplete surveys will not be recorded or retained.

Statistics and analysis

We will record the number of healthcare professionals whom we ask to complete each survey in order to calculate a response rate. We are aiming to survey 200 prescribing clinicians and 100 non-prescribers.

Categorical variables will be reported as counts and percentages. Differences between groups will be calculated and described with 95% confidence intervals only and will not include significance tests with P-values.

Data management

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

All study data will be downloaded from SurveyMonkey onto a Microsoft Excel spreadsheet. No identifying data will be collected or entered onto this spreadsheet.

Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to the Medical IDREC for written approval.

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

Finance and Insurance

Funding: Dr Alexandra Cairns' fellowship is funded as part of Professor McManus' NIHR professorship. The survey has not received any other funding.

Insurance: The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).



Publication policy

The study results will form part of Dr Alexandra Cairns' DPhil dissertation.

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the NIHR. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

Declaration of Helsinki

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

Appendix 1: Survey tool for prescribing clinicians

We are very grateful for you taking the time to complete this survey.

We are interested in surveying the views of doctors caring for **postnatal women** about the **adjustment of anti-hypertensive medication(s)** in women who have developed **hypertensive disorders of pregnancy**.

All the data and views collected are anonymous.

If you have any questions or feedback, please do not hesitate to contact us: alexandra.cairns@phc.ox.ac.uk

1. I confirm I have read the participant information sheet, and agree to participate in the survey.

I agree

☐

I disagree

☐

2. Please state the country in which you are working:

3. Please name the unit in which you are working:

4. What is your job title (*please select one option that best describes your job title*)?

Consultant Obstetrician

☐

Consultant Obstetric Physician

☐

General Practitioner

☐

Obstetric Associate Specialist

☐

Obstetric Registrar (ST3-7, SST)

☐

Obstetric Staff Grade

☐

Obstetric Physician Registrar

☐

General Practitioner Registrar (ST3 and above)

☐

Other (*please specify below*)

☐

5. What is your age?

21-29

☐

30-39

☐

40-49

☐

50-59

☐

60 or older

☐

6. What anti-hypertensive medication(s) do you use in the postnatal period (*select all that apply*)?

Labetalol

☐

Metoprolol (standard release)

☐

Metoprolol M/R

☐

Atenolol

☐

Nifedipine (standard release)

☐

Nifedipine M/R

☐

Amlodipine

☐

Captopril

☐

Enalapril

☐

Doxazosin

☐

Alpha-methyldopa

☐

Other (*please specify below*)

☐

7. Of the anti-hypertensive medications you have selected please state the **one medication** you use **most commonly** in the postnatal period?

8. When **down-titrating** medications in the postnatal period what is the **highest blood pressure** threshold at which you would **consider reducing the dose** of anti-hypertensive medications (*please select one systolic and one diastolic blood pressure*)?

SYSTOLIC

- < 110 ☐
- < 120 ☐
- < 130 ☐
- < 140 ☐
- < 150 ☐
- < 160 ☐
- Other (please specify below) ☐

DIASTOLIC

- < 60 ☐
- < 70 ☐
- < 80 ☐
- < 90 ☐
- < 100 ☐
- < 110 ☐
- Other (please specify below) ☐

9. When **up-titrating** medications in the postnatal period what is the **lowest blood pressure** threshold at which you would **consider increasing the dose** of anti-hypertensive medications (*please select one systolic and one diastolic blood pressure*)?

SYSTOLIC

- ≥ 170 ☐
- ≥ 160 ☐
- ≥ 150 ☐
- ≥ 140 ☐
- ≥ 130 ☐
- ≥ 120 ☐
- ≥ 110 ☐
- Other (please specify below) ☐

DIASTOLIC

- >120 ☐
- >110 ☐
- >100 ☐
- >90 ☐
- >80 ☐
- >70 ☐
- >60 ☐
- Other (please specify below) ☐

10. When you are **down-titrating medications** in response to the low blood pressure threshold you stated in question 7: **what proportion** would you normally **reduce a dose** of medication by (*choose the single answer which best describes your usual approach*)?*

- Approximately halve the dose of one medication ☐
- Next lower dose of one medication according to the prescribing formulary ☐
- Stop one medication completely ☐
- Stop all medications completely ☐
- My approach depends on the blood pressure ☐
- My approach depends on the patient's symptoms ☐
- I do not have a specific approach ☐
- Other (please specify below) ☐

11. When down-titrating multiple medications in the postnatal period how do you approach this (*choose the single answer which best describes your usual approach*)?*

- One medication at a time ☐
- All medications simultaneously ☐



I would choose which medication to reduce / stop based on the patient's side effects ☐

I do not have a specific approach because I don't often manage patients' down-titration in the postnatal period ☐

I do not have a specific approach; it depends on the individual patient ☐

Other (please specify below) ☐

12. Thank you very much for taking the time to complete this survey. Please leave any additional comments you have below.

**Questions in which the order of answers will be randomly generated*

Appendix 2: Survey tool for midwives and other non-prescribers

We are very grateful for you taking the time to complete this survey.

We are interested in surveying the views of healthcare professionals for caring for **postnatal women** about the **adjustment of anti-hypertensive medication(s)** in women who have developed **hypertensive disorders of pregnancy**.

All the data and views collected are anonymous.

If you have any questions or feedback, please do not hesitate to contact us: alexandra.cairns@phc.ox.ac.uk

1. I confirm I have read the participant information sheet, and agree to participate in the survey.

I agree

☐

I disagree

☐

2. Please state the country in which you are working:

3. Please name the unit in which you are working:

4. What is your job title (*please select one option that best describes your job title*)?

Hospital Midwife

☐

Community Midwife

☐

Health Visitor

☐

Practice Nurse

☐

Other (*please specify below*)

☐

5. What is your age?

21-29

☐

30-39

☐

40-49

☐

50-59

☐

60 or older

☐

6. What anti-hypertensive medication(s) do you have experience of caring for patients taking during the postnatal period (*select all that apply*)?

Labetalol

☐

Metoprolol (standard release)

☐

Metoprolol M/R

☐

Atenolol

☐

Nifedipine (standard release)

☐

Nifedipine M/R

☐

Amlodipine

☐

Captopril

☐

Enalapril

☐

Doxazosin

☐

Alpha-methyldopa

☐

Other (*please specify below*)

☐

7. Of the anti-hypertensive medications you have selected please state the **one medication** you have the **most experience** with?

8. What is the **highest blood pressure** threshold at which you would consider **referring** a patient to a prescribing clinician to consider **reducing the dose** of anti-hypertensive medication in the postnatal period (*please select one systolic and one diastolic blood pressure*)?

SYSTOLIC

- < 110 ☐
- < 120 ☐
- < 130 ☐
- < 140 ☐
- < 150 ☐
- < 160 ☐
- Other (please specify below) ☐

DIASTOLIC

- < 60 ☐
- < 70 ☐
- < 80 ☐
- < 90 ☐
- < 100 ☐
- < 110 ☐
- Other (please specify below) ☐

9. What is the **lowest blood pressure** threshold at which you would consider **referring** a patient to a prescribing clinician to consider **increasing the dose** of antihypertensive medication in the postnatal period (*please select one systolic and one diastolic blood pressure*)?

SYSTOLIC

- ≥ 170 ☐
- ≥ 160 ☐
- ≥ 150 ☐
- ≥ 140 ☐
- ≥ 130 ☐
- ≥ 120 ☐
- ≥ 110 ☐
- Other (please specify below) ☐

DIASTOLIC

- ≥ 120 ☐
- ≥ 110 ☐
- ≥ 100 ☐
- ≥ 90 ☐
- ≥ 80 ☐
- ≥ 70 ☐
- ≥ 60 ☐
- Other (please specify below) ☐

10. When you are caring for a patient on multiple anti-hypertensive medications in the postnatal period do you have a view about how this down-titration should be managed (*please select one option*)?*

- The choice of which medication should be reduced or stopped should be based on the patient's side effects ☐
- All medications should be reduced simultaneously ☐
- One medication should be reduced at a time (aiming to reduce the number of different medications as quickly as possible) ☐
- This should depend on the individual patient ☐
- I do not have a view about how this should be managed ☐
- Other (please specify below) ☐

11. Thank you very much for taking the time to complete this survey. Please leave any additional comments you have below.

**Questions in which the order of answers will be randomly generated*

References

1. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. *BMJ*. 2013;347:f6564.
2. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2011;118 Suppl 1:1-203.
3. American College of Obstetricians and Gynecologists. Diagnosis and management of preeclampsia and eclampsia. *ACOG Practice Bulletin*. ACOG Practice Bulletin No. 33; 2002.
4. Podymow T, August P. Postpartum course of gestational hypertension and preeclampsia. *Hypertens Pregnancy*. 2010;29(3):294-300.
5. National Institute for Health and Care Excellence. NICE Clinical Guideline 107: Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. 2011.
6. McManus RJ, Mant J, Bray EP, Holder R, Jones MI, Greenfield S, et al. Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial. *Lancet*. 2010;376(9736):163-72.
7. Pickering TG, Miller NH, Ogedegbe G, Krakoff LR, Artinian NT, Goff D, et al. Call to action on use and reimbursement for home blood pressure monitoring: executive summary: a joint scientific statement from the American Heart Association, American Society Of Hypertension, and Preventive Cardiovascular Nurses Association. *Hypertension*. 2008;52(1):1-9.

Amendment history

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



APPENDIX 8: Survey participant information sheet

This information will be provided as an attachment to the email invitation to participate.

Survey of healthcare professionals regarding adjustment of anti-hypertensive medication(s) in the postnatal period in women with hypertensive disorders of pregnancy

Researchers

Alexandra Cairns (Doctoral Research Student, Clinical Fellow)¹, Richard McManus (Professor of Primary Care)¹, Lucy Mackillop (Consultant Obstetric Physician)², Paul Leeson (Professor of Cardiovascular Medicine)³

1. Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, OX2 6GG
2. Nuffield Department of Obstetrics and Gynaecology, University of Oxford
3. Cardiovascular Clinical Research Facility, University of Oxford

Telephone: 0800 9150045

Email: alexandra.cairns@phc.ox.ac.uk

Preamble and Definitions:

This is an online questionnaire survey about the adjustment of anti-hypertensive medication(s) in women with hypertensive disorders of pregnancy during the postnatal period.

You have been asked to part as you are a healthcare professional who has been involved with managing postnatal women with hypertensive disorders of pregnancy.

Hypertensive disorders of pregnancy: gestational hypertension and pre-eclampsia

Gestational hypertension: new-onset raised blood pressure (≥ 140 mmHg systolic or ≥ 90 mmHg diastolic beyond 20 weeks gestation)

Pre-eclampsia: new-onset raised blood pressure (≥ 140 mmHg systolic or ≥ 90 mmHg diastolic beyond 20 weeks gestation) WITH significant proteinuria (≥ 300 mg per 24 hours)

What will happen if you take part?

The survey will take about 10 minutes to complete.

Your answers are important to us, and will help us to understand how healthcare professionals approach this clinical problem. We are hoping to use the results of this survey to assist us in designing an approach to anti-hypertensive medication adjustment during the postnatal period for use in a clinical trial of self-management of postnatal anti-hypertensive treatment.

All responses will be treated in complete confidence and your answers will only be seen by the research team. No identifiable data will be collected in the course of the survey.

The research has been reviewed by, and received ethics clearance through, the University of Oxford Central University Research Ethics Committee.



The University of Oxford is committed to the dissemination of its research for the benefit of society and the economy and, in support of this commitment, has established an online archive of research materials. This archive includes digital copies of student theses successfully submitted as part of a University of Oxford postgraduate degree programme. Holding the archive online gives easy access for researchers to the full text of freely available theses, thereby increasing the likely impact and use of that research. If you agree to participate in this project, the research will be written up as part of a thesis. On successful submission of the thesis, it will be deposited both in print and online in the University archives, to facilitate its use in future research. The thesis will be published with open access.

No risks are anticipated from taking part in the study. If you feel uncomfortable at any stage prior to completion you can withdraw from the study altogether. If you decide to withdraw before you complete the survey, your answers will not be recorded.

By beginning the survey, you acknowledge that you have read this information and agree to participate in this research. You are free to choose to participate, and to withdraw your participation at any time, for any reason, without penalty.

How do I consent to take part in the study?

The first page of the online survey will contain the consent form. You will need to read 5 consent statements, and then select 'I agree' before being able to begin completion of the study. If you select 'I disagree' you will be automatically disqualified from the study.

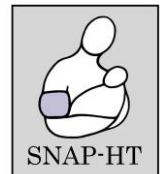
What if there is a problem?

If you have a concern about any aspect of this project, please speak to the relevant researcher (Alexandra Cairns, telephone 0800 9150045), who will do her best to answer your query. The researcher should acknowledge your concern within 10 working days and give you an indication of how she intends to deal with it.

If you remain unhappy or wish to make a formal complaint, please contact the chair of the Research Ethics Committee at the University of Oxford (Chair, Medical Sciences Inter-Divisional Research Ethics Committee; Email: ethics@medsci.ox.ac.uk; Address: Research Services, University of Oxford, Wellington Square, Oxford OX1 2JD). The chair will seek to resolve the matter in a reasonably expeditious manner.

Appendix 9: SNAP-HT blood pressure monitoring instructions

Self-maNAgement of Postnatal anti-Hypertensive Treatment SNAP-HT Trial Development Pilot Study: Home Blood Pressure Monitoring



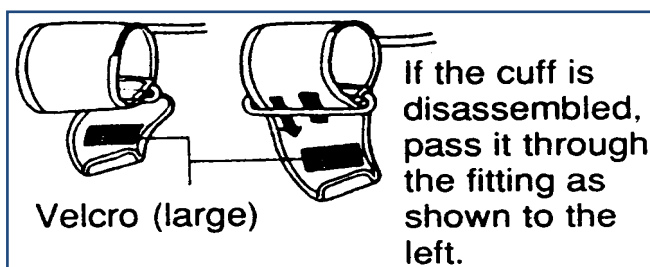
You will take one set of blood pressure (BP) readings each day: please take them at approximately the same time each **morning**. Always use the **same arm** for the readings (this will **normally the left arm**).

If you have any difficulties, please contact the research team by telephoning: 0800 9150045 or emailing: alexandra.cairns@phc.ox.ac.uk.

Before you begin make sure you:

- Do not need to use the toilet.
- Have not just eaten a large meal.
- Have not drunk caffeine, smoked or exercised within the last 30 minutes.
- Are wearing loose clothing with sleeves that roll up easily and do not feel tight when rolled up (you will need to fit the cuff onto your bare arm).
- Have rested sitting quietly for about 5 minutes before you begin. Make sure you remain somewhere quiet where you will not have to speak when you take your BP.
- Have your mobile telephone next to you, and also a watch or clock.

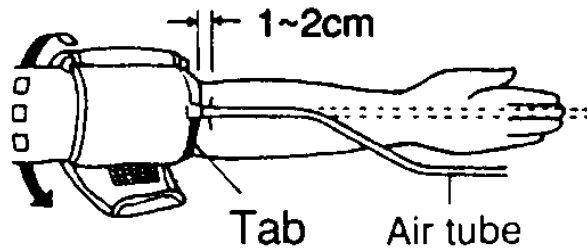
How to take your BP (Microlife WatchBP® Home):



- Sit on a comfortable chair with your back supported and both feet flat on the floor. You should rest for 5 minutes before beginning to take blood pressure readings.

- Slip the cuff onto your arm (Use your non-dominant arm (usually left arm) unless otherwise advised) so that the air tube is located at the wrist side.
- Adjust the edge of the cuff so that it is about ½ inch (1-2 cm) above the inside of the left elbow joint.

Fold the cuff back at the fitting.



- Tighten the cuff around the arm without leaving a gap between the cuff and the arm and secure using the velcro
- Rest your arm on a table or across your lap with your hand slightly open and the palm facing upward
- If the tube from the cuff has become unplugged then insert the tube plug into the air jack on the left hand side of the monitor

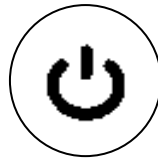


- Check that the display reads 'USUAL' in the top left hand corner. If it reads 'DIAG', slide the switch on the right hand side of the monitor to the right (U)



Slide switch to right

- Once the machine is set up and you have the cuff in the correct position, and you are ready to start, press the start button on the front of the machine to take a reading.



- Relax and do not talk or move your arm until the measurement is completed
- Each time you measure your blood pressure you will get three readings: SYS (systolic), DIA (diastolic) and PUL (pulse). You only need the SYS and DIA readings.



- You need to measure your blood pressure twice, **at least one minute apart** and record both the readings
- In the >1 minute rest, please remain **seated and relaxed**
- You will record the SYS and DIA readings and communicate the second SYS and DIA readings with a central server using either the smart phone app or text messaging system.

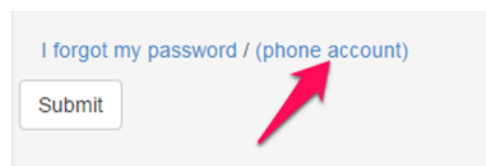
What to do if your blood pressure monitor does not work?

Failure	Possible causes	Hint
Error message: ERR 1	Signal too weak	Re-position the cuff and repeat the measurement.
Error message: ERR 2	Error signal e.g. due to movement of arm during reading	Repeat measurement keeping still: do not move arm and do not speak
Error message: ERR 3	No pressure in cuff e.g. leak may have occurred or cuff is fitted too loosely	Check cuff is properly connected to monitor. Check cuff is fitted correctly and repeat measurement.
Error message: ERR 5		Read instructions for taking measurements correctly and repeat measurement
Error message: HI		Relax for 5 minutes and repeat the measurement
Error message: LO		Relax for 5 minutes and repeat the measurement
Your clothing has constricted flow		Remove item of clothing that has caused constriction
There is still air in the cuff when the monitor is switched off		Call the study helpline
BP readings are very different to normal		Relax for 5 minutes and repeat the measurement
The display is not lit up		Replace the batteries in the machine
The cuff seems too small or too large		Call the study helpline to check you are using the correct sized cuff

APPENDIX 10: SNAP-HT Telemonitoring manual for participants

LOGIN: Username = mobile telephone number
447*****

PASSWORD: This will be given to you by the research team and sent to your mobile telephone. This can be changed on the website.



FREQUENCY OF BP READINGS:

On treatment / first week off treatment: take 2 readings daily in the morning, and submit the second reading via the SMS service or app

Off treatment: weekly readings

REPEAT READINGS:

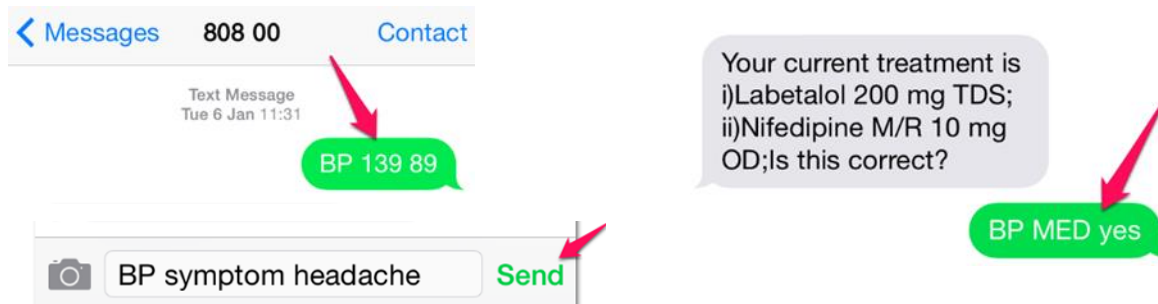
If your blood pressure is very high or very low, you will be asked to repeat the reading. Please sit quietly for 5 minutes, then take one reading and send this via the SMS service or the app.

MISSED READINGS:

If you do not submit a number of consecutive blood pressure readings you will be sent a reminder message. If you still do not send a blood pressure a member of the research team will contact you. This is to ensure your safety during the trial.

SMS MESSAGES: Send to **80800**

ACTION	COMMAND
Sending BP reading	BP sys dia e.g. BP 134 84
Responding to medication check	BP med yes OR BP med no
Sending adverse event	BP symptom __ e.g. BP symptom fever



MEDICATION PLANS:

Your first plan will be plan 'A'. The medications you are discharged from hospital on will be step 'A0'. The final step of your medication plan will be to STOP all treatment. If at any stage during the trial you require a medication increase, you will have a new plan (plan 'B') created to take account of this.

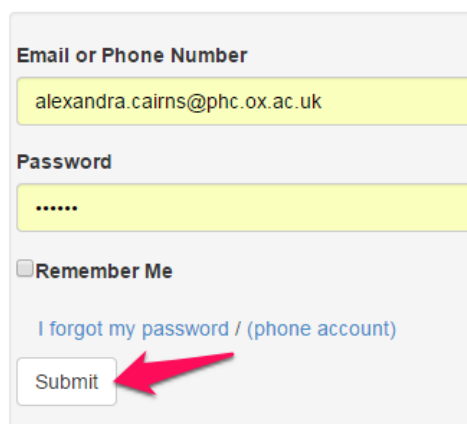
APPENDIX 11: SNAP-HT Telemonitoring manual for research team

SNAP-HT Telemonitoring: *Research Team Manual*

1. Login (all)

Your username for the smartphone app and website will be your email address. Your password will be given to you by the Chief Investigator.

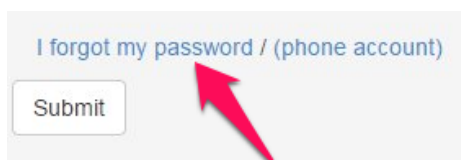
Login



The screenshot shows a login form with the following elements:

- Email or Phone Number:** A text input field containing the email address `alexandra.cairns@phc.ox.ac.uk`.
- Password:** A text input field with masked characters (dots).
- Remember Me:** A checkbox that is currently unchecked.
- Forgot Password Link:** A blue link that reads "I forgot my password / (phone account)".
- Submit Button:** A button labeled "Submit". A red arrow points to this button.

To login enter your username and password and click 'submit'. If you forget your password please click on 'I forgot my password' on the login page. Then enter your registered email address and click 'submit' and a new password will be sent to your email.



The screenshot shows a close-up of the "I forgot my password / (phone account)" link and the "Submit" button. A red arrow points to the link.

To change your password to something more memorable please log in to the website and click on 'change password' at the top of the home screen.

2. Registering participants (all)

The home screen will be the 'Patients Dashboard'. At the top of this screen is a blue button 'add new patient'. To add a new participant please click this button.

Hello [Alex\(admin\)/](#) [logout](#) [Users](#) [Areas](#)

PATIENTS DASHBOARD

[Add New Patient](#)

You will then be required to enter the following information:

Add Patient

Study ID

Area

Select Area

First Name

Last Name

Phone Number

Delivery Date

Out Of Hospital Date

Save Patient

Cancel

If you do not know the actual date of discharge please enter the planned date, as this can be amended later. Then click 'save patient'.

You will then be asked to enter step A0 of their medication plan: this is their current medication. This will allow the Chief Investigator to create a medication adjustment plan.

- Click 'edit'

Patient Details

Medication Plan Step A0

Patient created. Please add drugs for step 0.

Editing Drugs for step A0

Name	Dose	Frequency	Notes
edit			

- Then click 'add row' and complete the details of their first medication from the drop down lists

- Repeat this for up to three different medications
- Then click ‘save’

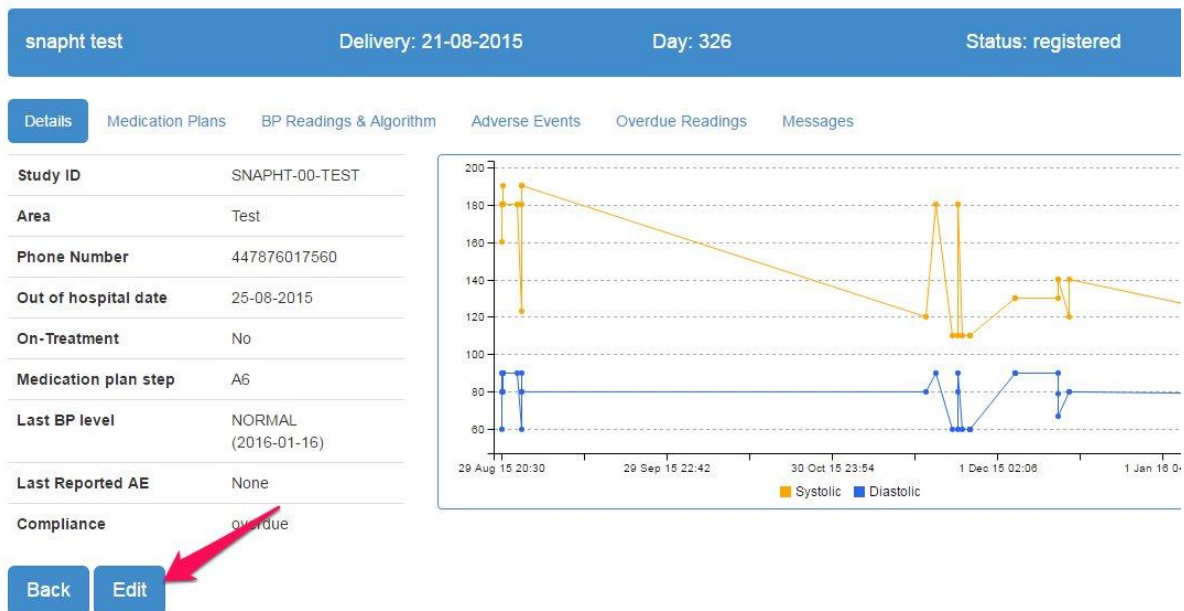
The participant should then appear on the patient list.

Patients will be automatically assigned the status ‘registered’ and will not be activated at this stage.

The participant’s password will be sent to your email account.

3. Activating patients

After a patient has been registered and then discharged from hospital after birth they then need to be activated: to do this click on a participant’s name on the patient list. Once the participant’s details are open click the ‘Edit’ button.



On the screen that opens enter the patient’s discharge date, change their status to ‘active’ on the scroll down menu and then click on ‘Save Patient’.

4. Reviewing participants details (all)

The tab at the top of the screen labelled 'Patients' will enable you to see a list of all patients (Area Coordinators will only be able to see patients from their area).

Study ID	Name	Compliance	Consistency	AE	Thu	Fri	Sat	Sun	Mon	Tue	Wed	Treatment	Area
SNAP-11-001	Penelope Perfect	On-track			 (1)	 (1)	 (1)	 (1)	 (1)	 (1)	 (1)	A3	Oxford
SNAP-11-002	Annabel Anxious	On-track			 (1)	 (1)	 (2)	 (1)	 (2)	 (1)	 (2)	off	Banbury
SNAP-11-003	Fiona Forgetful	On-track			 (0)	 (0)	 (0)	 (1)	 (1)	 (1)	 (1)	A2	Reading

This list will contain the following details:

- Study ID
- Name
- Compliance (i.e. submitted readings up to date)
- Consistency (is what medication(s) the participant thinks they are taking consistent with the current medication step according to the telemonitoring system)
- Any reported and unresolved adverse events (dark blue flag if reported, light blue flag if research team have attempted to resolve this, but been unable to contact the participant 'unresolved')
- Blood pressures over the last 7 days (colour coded)
- Medication step
- Area

By clicking on a participant's name you will be able to see all the information about that participant.

Penelope Perfect

Delivery: 01-01-2015

Day: 19

Status: active

Details

Medication Plans

BP Readings & HT Algorithm

SMS

Adverse Events

Overdue Readings

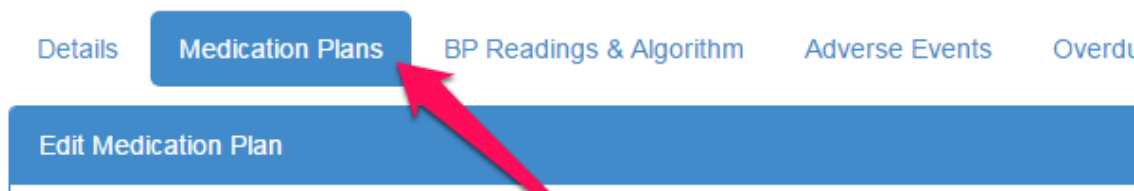
There will be 6 tabs across the top of the next page:

- Details (currently displayed)
- Medication plans (current and any historic, inactive plans)
- BP readings and HT algorithm
- SMS history
- Adverse events
- Overdue readings

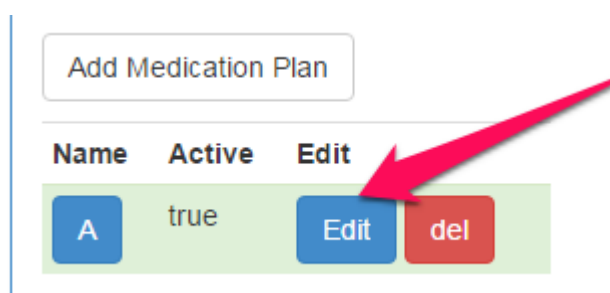
Area Co-ordinators will only be able to view this information. They will not be able to edit medication plans, or to resolve overdue readings, adverse events or inconsistent medication.

5. Creating medication plans (Administrators only)

Medication plans will be created by the Chief Investigator during the trial. Once the discharge medications (step A0) have been entered by the trial team member registering the patient the CI will then be able to create the plan.



The medication plan tab is selected and then the 'Edit' button next to plan A is selected.



Then the letter 'A' needs to be clicked to allow steps to be added. The 'Add step' button is used to add the required steps to the final step before STOP. Within a step the each drug (with dose and frequency) will need to be added separately.

Add Medication Plan

Name	Active	Edit
A	☒	save cancel

Medication Plan A Details

Step	Drug, Dose, Freq.
A.0	Labetalol 400 mg 1x daily
A.1	Labetalol 200 mg 1x daily
A.2	Metoprolol M/R 12.5 mg 1x daily
A.3	Metoprolol 400 mg 3x daily
A.4	Metoprolol 200 mg 2x daily
A.5	Enalapril 400 mg 2x daily

Steps for Medication Plan A

Step	Start	Consistent	Consistency status	Description	Edit
0	8/24/15 6:25 PM	No	resolved		Resolve del Drugs (1)
1	11/25/15 9:46 PM		Not Reported		del Drugs (1)
2	11/25/15 9:52 PM		Not Reported		del Drugs (1)
3	11/25/15 10:03 PM		Not Reported		del Drugs (1)
4	11/25/15 10:05 PM	Yes	resolved		del Drugs (1)
5	12/4/15 8:34 AM		Not Reported		del Drugs (1)
6 (Stop)	12/4/15 8:34 AM	Yes	resolved		del

Add Step

Move to next step

Subsequently new medication plans can be created using the 'Add Medication Plan' button, and which plan is 'active' can be altered by checking the box (see above image). An existing medication plan can also be altered using the Edit button.

6. Resolving overdue readings (Administrators only)

If a participant has an overdue reading this will be displayed on the patient list as a red flag. Participants whose readings are up to date will have ‘on-track’ displayed. Participants whose readings are overdue, but not so far overdue as to generate a flag will have a lightbulb icon displayed. This signifies that a participant has been sent an automatic reminder message.

Participants who have not sent a BP reading in response to the reminder message will have a flag generated. This signified the need to contact a participant. A red flag will be shown for reported overdue readings. If the research team have attempted to resolve this, but been unable to contact a participant, an orange flag will be shown: ‘unresolved’).

To resolve an overdue reading:

- Click on a participant’s name in the patient list
- Click on the ‘overdue readings’ tab

HT Algorithm SMS Adverse Events **Overdue Readings**

- Click ‘edit’ alongside the reported overdue reading

Overdue Readings				
Date	Resolution Status	Resolution Description	Resolution Date	Edit
2015-01-08 16:25:01	resolved	patient is now compliance with sending BP	14-01-2015 14:45	Edit
2015-01-16 10:50:01	reported		01-01-1970 00:00	Edit

- Contact the patient by telephone
- Amend resolution status to ‘resolved’ if successfully contact participant, or ‘unresolved’ if attempted to contact participant, but not successful

2015-01-16 10:50:01	resolved	patient contacted. Will send	01-01-1970 00:00	save cancel

- Amend resolution description to contain details of resolution
- Then click ‘save’

7. Resolving adverse events (Administrators only)

If a participant has reported an adverse event, or one has been generated automatically (BP $\geq$ 160 /110 or < 90 / 50) this will be displayed on the patient list.

Reported adverse events will be shown as a dark blue flag.

SNAP-11-005

Wendy
Wobbly

On-track


 (1)

‘Unresolved’ adverse events will be shown as a light blue flag (this indicates that the research team has attempted to contact a participant, but not yet been successful).

Once adverse events have been resolved the flag will disappear.

To resolve an adverse event:

- Click on a participant’s name in the patient list
- Click on the ‘adverse events’ tab



- Click ‘edit’ alongside the reported adverse event

Adverse Events							
Date	Source	Type	Patient Description	Resolution Status	Resolution Description	Resolution Date	Edit
08-01-2015 13:42	sms	BP>=160/110	BP 159 112	resolved	Patient contacted and medication changes addressed	09-01-2015 15:19	Edit del

- Contact the patient by telephone
- Decide if serious AE and complete form if yes
- Amend resolution status to ‘resolved’ if successfully contact participant, or ‘unresolved’ if attempted to contact participant, but not successful

08-01-2015 13:42

sms

BP>=160/

▼

BP 159 1

resc

▼

Patient contacted and med

09-01-2015 15:19

save

cancel

- Amend resolution description to contain details of resolution
- Then click ‘save’

8. Resolving inconsistent medications (Administrators only)

On-track   Harriet Headache (0)  (1)

A green flag will appear in the consistency column if the medication check is answered 'no'.

Click on the participant's name.

Then select the Medication Plans tab:

Medication Plans  GP Readings

Select the current (active) medication plan by clicking on the letter:

Name	Active	Edit
A	false	del
B	true	Edit del



Medication Plan B Details

Step	Drug, Dose, Freq.
B.0	Labetalol 400 mg QDS
B.0	Captopril 25 mg BD

Step: 0 1 2 3 4

The current medication step will be highlighted in green. If there is an inconsistency in the 'Consistent' column it will read 'No'. Click on the blue button 'resolve' in order to amend this:

Step	Start	Consistent	Consistency status	Description	Edit
0	1/9/15 10:34 AM	Yes	resolved		del Drugs (2)
1	1/17/15 2:19 PM	No	reported		Resolve del Drugs (2)

If necessary add a new medication plan to take account of changes.

9. Adding / editing users (Administrators only)

Administrators will be able to add users: to do this click on the 'users' tab at the top of the screen, and then on the 'add user' button.

10. Being upgraded to administrator

At stages during the trial, after discussion with the Chief Investigator it may appropriate that area co-ordinators are temporarily upgraded to 'administrator' status. This will allow them to:

- View participants from all areas
- Amend medication plans
- Resolve overdue readings, adverse events and inconsistent medications
- View users (and edit / delete)
- Receive daily emails containing details of:
 - Reported and unresolved overdue reading flags
 - Reported and unresolved adverse event flags
 - Inconsistent medications following medication checks

APPENDIX 12: SNAP-HT Feasibility study protocol

Study Title: Self-management of postnatal anti-hypertensive treatment: a trial development pilot study

Internal Reference Number / Short title: SNAP-HT trial development pilot study

Ethics Ref: 14/SC/1316

ClinicalTrials.gov Identifier: NCT02333240

Date and Version No: 06/06/2016 V5.1

Chief Investigator: Dr Alexandra E Cairns, University of Oxford

Investigators:

Professor Richard McManus, University of Oxford

Professor Paul Leeson, Cardiovascular Clinical Research Facility John Radcliffe Hospital

Dr Lucy Mackillop, Oxford University Hospitals NHS Trust

Dr Susan Lloyd, Northampton General Hospital NHS Trust

Dr Mark Selinger, Royal Berkshire Hospital NHS Foundation Trust

Miss Felicity Ashworth, Buckinghamshire Healthcare NHS Trust

Dr Katherine Tucker, University of Oxford

Professor John Powell, University of Oxford

Dr Jasmine Harvey, University of Oxford

Sponsor: University of Oxford

Funder: NIHR Collaborations for Leadership in Applied Health Research and Care

Chief Investigator Signature:



No conflicts of interest.

Confidentiality Statement

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

TABLE OF CONTENTS

1.	SYNOPSIS	4
2.	ABBREVIATIONS.....	5
3.	BACKGROUND AND RATIONALE.....	5
4.	OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS	7
5.	STUDY DESIGN	8
6.	PARTICIPANT IDENTIFICATION	9
6.1.	Study Participants.....	9
6.2.	Inclusion Criteria.....	9
6.3.	Exclusion Criteria	10
7.	STUDY PROCEDURES	10
7.1.	Recruitment.....	10
7.2.	Informed Consent.....	11
7.3.	Visit 1: Screening and Eligibility Assessment.....	11
7.4.	Randomisation, blinding and code-breaking.....	12
7.5.	Visit 2: Baseline.....	12
7.6.	Visits 3-7: Follow-up	14
7.7.	Discontinuation/Withdrawal of Participants from Study.....	15
7.8.	Definition of End of Study	15
8.	INTERVENTIONS.....	15
8.1.	Self-management of blood pressure	15
9.	SUB-STUDIES.....	16
9.1.	Patient experience structured interviews	16
9.2.	Vascular risk.....	17
10.	SAFETY	18
10.1.	Definition of Serious Adverse Events	18
10.2.	Expected Serious Adverse Events.....	18
10.3.	Recording and Reporting Procedures for Adverse Events and Serious Adverse Events	19
11.	LONE WORKING POLICY	19
12.	STATISTICS AND ANALYSIS.....	19
12.1.	Description of Statistical Methods	19
12.2.	The Number of Participants	20
12.3.	Analysis of Outcome Measures	20

12.4.	Interim analysis.....	20
13.	DATA MANAGEMENT	20
13.1.	Access to Data	20
13.2.	Data Recording and Record Keeping	21
14.	QUALITY ASSURANCE PROCEDURES	21
15.	ETHICAL AND REGULATORY CONSIDERATIONS.....	21
15.1.	Declaration of Helsinki.....	21
15.2.	Guidelines for Good Clinical Practice	21
15.3.	Approvals.....	21
15.4.	Reporting	22
15.5.	Participant Confidentiality.....	22
15.6.	Expenses and Benefits.....	22
15.7.	Other Ethical Considerations.....	22
16.	FINANCE AND INSURANCE	23
16.1.	Funding	23
16.2.	Insurance	23
17.	PUBLICATION POLICY.....	23
18.	REFERENCES	24
19.	APPENDIX A: STUDY FLOW CHART	25
20.	APPENDIX B: SCHEDULE OF STUDY PROCEDURES.....	26
21.	APPENDIX C: AMENDMENT HISTORY	27
22.	APPENDIX D: Blood pressure thresholds for self-management.....	28

1. SYNOPSIS

Study Title	Self-management of postnatal anti-hypertensive treatment trial development pilot study	
Internal ref. no. / short title	SNAP-HT trial development pilot study	
Study Design	Non-blinded, randomised, controlled trial-development pilot study	
Study Participants	Women in the postnatal period, with gestational hypertension or pre-eclampsia requiring on-going anti-hypertensive treatment.	
Planned Sample Size	100 women	
Planned Study Period	December 2014 – March 2016 (15 months)	
	Objectives	Outcome Measures
Primary	Feasibility of study	Recruitment rate Retention rate Loss to follow up rate Withdrawal rate Compliance/adherence rate in the self-monitoring group
Secondary	Does BP self-management postpartum period improve BP control?	Number of blood pressure readings in target range BP at day 10, 4 weeks, 6 weeks, 12 weeks and 26 weeks postpartum Number of urgent visits, and timing of these, to GP or hospital requiring medication increase due to BP > 150/100, or medication decrease due to BP < 100 systolic
	Can BP self-management postpartum reduce postnatal readmissions to hospital with poorly controlled hypertension?	Postnatal readmission rate
	To assess patient experience of self-management of blood pressure in the postpartum period.	EQ-5D-5L health questionnaire results Structured interviews (participants)
	To assess vascular outcomes, and determine whether better blood pressure control correlates with improved vascular risk markers	Cardio-ankle vascular index Radial arterial tonometry Capillaroscopy
	Safety	Reporting of serious adverse events Side effect reporting
Exploratory analysis	To explore percentage time spent in range as a marker for blood pressure control in this setting	Assess percentage time spent in target BP range in both groups; use the home monitoring data from the intervention arm to explore the validity of this measure and

		the relationship between the trial blood pressure readings taken at two time points
	Setting BP thresholds for future trials	Difference between home and clinic BP recordings

2. ABBREVIATIONS

BP	Blood Pressure
CAVI	Cardio ankle vascular index
CDMS	Computerised Data Management System
CI	Chief Investigator
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NRES	National Research Ethics Service
PCCTU	Primary Care Clinical Trials Unit, University of Oxford
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMG	Trial Management Group

3. BACKGROUND AND RATIONALE

Gestational hypertension, defined as blood pressure (BP) of $\geq 140/90$ mmHg, affects between 6 and 15% of pregnancies. A recent population-based retrospective study in the USA found the rate of pre-eclampsia (BP $\geq 140/90$ mmHg and new onset significant proteinuria ≥ 300 mg/24hr) to be 3.4% (1). In England in 2008 there were 665,800 pregnancies, and NICE estimates that 89,900 of these were affected by gestational hypertension (2).

There has been considerable focus, both within the primary literature and from the NICE guidance, on BP control during pregnancy, especially with respect to pregnancy outcome. However, it has been shown

that severity of hypertension in later life is associated with the degree of hypertension during the first six weeks postpartum (3). Work is on-going which suggests that those with above-average BP at six weeks postpartum have an approximately 30% increase in aortic stiffness. NICE guidance highlights that very few clinical studies have addressed the management of BP postpartum and clinical care is typically to continue antepartum BP medication and monitor BP in the community with a focus on prevention of over-treatment (4).

Previous work by Prof McManus' group has shown that self-monitoring and self-titration of anti-hypertensive medications in essential hypertension in the non-pregnant population is both feasible and more effective than usual care. The TASMINH2 randomised controlled trial demonstrated that self-management of BP in patients with poorly controlled essential hypertension resulted in a statistically significant reduction in mean systolic BP compared with patients undergoing usual care (difference between groups at 12 months 5.4mmHg, $P = 0.0004$) (5). Results from a further RCT in patients at high cardiovascular risk have demonstrated an even greater effect of self-management in this cohort (TASMIN-SR) (6). No research to date suggests that this intervention should pose any risks to participants i.e. that blood pressure control should be impaired through self-monitoring and self-management.

The proposed study aims to apply this experience to postpartum women with gestational hypertension and pre-eclampsia where both high and low BP can lead to adverse outcomes, and where detection of on-going hypertension is essential. Most women will be treatment-free by 3 months postpartum (7). This poses an additional challenge in terms of how best to manage this down-titration, and use of the self-management approach to assist with this will also be addressed.

To date research in self-monitoring and self-management of hypertension in non-pregnant patients has shown that it is feasible, acceptable to patients and produces better BP control when compared with conventional monitoring in a clinic setting (5). The results of this study will be utilised in the planning of a large scale randomised controlled trial investigating self-management of BP in the postpartum period. Women with medicated gestational hypertension and pre-eclampsia would seem to be an ideal cohort in whom to apply this work: the disease has, in general, a limited time course meaning that intensive monitoring is more reasonable and more likely to be adhered to. Pregnant women are by definition in a younger age group than the majority of those with essential hypertension, and may be more comfortable with the use of technology to assist in disease monitoring. Women might also be more driven in the setting of a recent pregnancy to take greater responsibility for their health.

BP control in the postpartum period can be challenging due to other pressures on women and healthcare professionals, and as a result of the need to wean medication appropriately in response to changing BP over a relatively short time-frame. If self-monitoring in the postpartum period proves to be a feasible, acceptable and a successful strategy for management of BP, it could lead to a reduction in the length of inpatient stay, readmissions and the number of postpartum visits, with cost-saving implications for both primary and secondary care. Furthermore as the importance of BP control in the immediate postpartum period has already been demonstrated to affect women's cardiovascular risk up to 15 years after delivery, any strategy, which successfully increases women's adherence to an effective treatment regimen, has the potential to influence their healthcare needs well into the future.

This study is a pilot study: it has been set up in order to inform the planning of a large-scale multi-centre randomised controlled trial by testing the feasibility of methods and procedures for later use on a large scale. We want to increase our experience of applying this management approach in this subset of

patients; to select the most appropriate primary outcome measure and to estimate the effect size of this intervention; to assess recruitment potential; and to evaluate feasibility of coordinating this trial across several centres. The primary objective of the large-scale trial will be to determine whether the self-management approach can improve blood pressure control in women with medicated hypertensive disorders of pregnancy in the postnatal period.

4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Specific objectives and outcome measures for this pilot study are listed in the table below. The overall objectives of this pilot study are (8, 9):

- **Process:** recruitment and retention rates; acceptability of the intervention; randomisation procedure; integrity of the protocol
- **Resources:** testing of questionnaires; length of time required to conduct study procedures
- **Management:** testing of data collection forms and data management system; centre willingness and capacity;
- **Scientific:** selection of the most appropriate outcome measure; safety of the intervention; were any important variables omitted; estimate of the treatment effect

Objectives	Outcome Measures/Endpoints	Time point(s) of evaluation of this outcome measure (if applicable)
Primary Objective		
Feasibility of study	Recruitment rate <i>Number of participants randomised / number of consenting participants</i> <i>Number of participants randomised / number of potential participants approached</i> Retention rate <i>Number of participants completing trial follow up / number of participants randomised</i> Attrition rate <i>Number of participants lost to follow-up or withdrawn / number of participants randomised</i> Compliance rate <i>Number of study visits attended / total number of intended study visits</i>	End of trial period
Secondary Objectives		
To investigate whether self-management of hypertension in the postpartum period leads to improved blood pressure control	Blood pressure at day 10, 4 weeks, 6 weeks, 12 weeks and 26 weeks postpartum Number of blood pressure readings in target range 'Time to event': number of urgent visits, and timing of these, to GP or hospital requiring medication increase due to BP > 150/100, or medication decrease due to BP < 100 systolic	End of trial period

To assess whether self-management of blood pressure in the postpartum period can reduce postnatal readmissions to hospital with poorly controlled hypertension.	Postnatal readmission rate in each group <i>Number of postnatal readmissions / number of randomised participants</i>	End of trial period
To assess patient experience of self-management of blood pressure in the postpartum period	EQ-5D-5L health questionnaire results Structured interviews (participants)	End of trial period End of trial period for those participants in patient experience sub-study
To determine whether better blood pressure control correlates with improved vascular risk markers	Arterial stiffness indices (CAVI and arterial tonometry) Microvascular changes (capillary density)	End of trial period for those participants in vascular sub-study
Safety	Reporting of serious adverse events Reporting of side effects	Ongoing throughout trial period
Exploratory analysis		
To explore percentage time spent in range as a marker for blood pressure control in this setting.	Assess percentage time spent in target BP range in both groups, and use the home monitoring data from the intervention arm to explore the validity of this measure and the relationship between the trial blood pressure readings taken at two time points	End of trial period
Setting BP thresholds for future trials	Difference between home and clinic BP recordings	End of trial period

5. STUDY DESIGN

Non-blinded randomised controlled trial. The participants will not be blinded as the nature of the intervention precludes this. All results will be analysed on an intention to treat basis. In order to assist with recruitment numbers, and to assess the feasibility of running a multi-centre trial, we are planning to run this study within several hospitals local to Oxford.

Women with gestational hypertension or pre-eclampsia requiring on-going anti-hypertensive medication in the postpartum period will be randomised to one of two treatment arms: usual care, or self-management of blood pressure.

Women randomised to usual care will have their blood pressure monitored by their community midwife, and will have their anti-hypertensive medication adjusted by their general practitioner.

Women randomised to self-management of blood pressure will have an individualised medication adjustment schedule (based on NICE guidance for medication adjustment postpartum). They will be provided with, and taught to use, a validated home blood pressure monitor, and perform daily blood pressure readings until they have discontinued treatment. The monitor used will be Microlife WatchBP® Home as these have been validated for use in pregnancy. These monitors have been purchased by the Nuffield Department of Primary Care Health Sciences. Women will be provided with written instructions about use of the monitor. When treatment is discontinued we will ask them to continue weekly blood pressure measurements for 1 week, and provided these are normal (<140/90) they will then be asked to check their blood pressure weekly for the remainder of the trial period. The self-monitoring BP data will

be collated centrally through the use of a smart phone app or text messaging based system. This service will respond to participants regarding the level of their BP and what action is required (if any). At the end of the study period the data from the home BP monitors will also be uploaded to the trial database.

These blood pressure readings will replace those that would normally be taken by their community midwives. If women still require additional support from the GP or community midwife postpartum for other medical, psychiatric or social issues then this will continue.

All women will be followed up at 10 days, then 4, 6, 12 and 26 weeks postpartum and have their blood pressure measured by one of the study team. If women still require anti-hypertensive treatment at 6 weeks postpartum, they will be offered referral to the specialist hypertension clinic.

At the baseline visit, and 12 and 26 week follow up women will be weighed using a standardised set of scales. This is in order to evaluate whether the extent and speed of return to booking weight (a mark of pre-pregnancy weight) correlates with resolution of gestational hypertension.

Women from each group will be asked to complete the EQ-5D-5L Health Questionnaire to assess their quality of life at screening (visit 1), 6 weeks (visit 5) and 26 weeks (visit 7). Additionally we will conduct optional structured interviews with women from both groups in order to assess their experience of management of blood pressure in the postpartum period. Some baseline data will be collected at visit 1 (screening), and structured interviews will be done at the 4 (visit 4) and 26 week (visit 7) visits. We aim to recruit a minimum of 50% of participants in each group (i.e. 50 women, 25 from each group) into this sub-study.

Gestational hypertension and pre-eclampsia are both associated with future cardiovascular disease in the mother (10, 11). To follow on from the work that suggests that those with above-average BP at six weeks postpartum have an approximately 30% increase in aortic stiffness; we are planning to conduct a sub-study to analyse markers of vascular risk in women from both groups. As it may be assumed that the baseline characteristics of the two groups are then similar, if we demonstrate a treatment effect from the intervention, then it will allow us to analyse the relationship between blood pressure control in the postnatal period and markers of vascular risk to help determine if it is the severity of pathology or effectiveness of control that determines long term outcome. Women will consent to an optional extended visit at baseline (or day 10) and 12 weeks where measures of arterial stiffness and capillary density will be taken. Additionally in women who consent to participating in this element of the study we will take a blood sample to measure circulating biomarkers relevant to cardiovascular health. We aim to recruit a minimum of 15 women from each group into this sub-study.

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

Women with a diagnosis of gestational hypertension or pre-eclampsia, who require on-going antihypertensive medication in the postpartum period.

6.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.

- Female, aged 18 years or above.*
- Women with **gestational hypertension** (new-onset BP $\geq$ 140/90mmHg) or **pre-eclampsia** (new onset BP $\geq$ 140/90mmHg and significant proteinuria $\geq$ 300mg/24hr), prior to their discharge from hospital post-delivery.
- Require antihypertensive medication during pregnancy, which needs to continue in the postpartum period.

*The justification for the lower age limit is that we do believe that in this pilot study additional benefit would be derived from conducting the research in under-18s, compared with conducting it in adults (as per guidance from the General Medical Council) (12).

6.3. Exclusion Criteria

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

- Hypertension prior to pregnancy.
- Poor English language skills.
- More than three anti-hypertensive agents at discharge from hospital postpartum.

7. STUDY PROCEDURES

7.1. Recruitment

Women undergoing obstetric care at the John Radcliffe Hospital (Oxford), Horton General Hospital (Banbury), Royal Berkshire Hospital (Reading), Stoke Mandeville Hospital (Aylesbury) and Northampton General Hospital (Northampton) will be approached during pregnancy. The study will be advertised through the use of posters in patient areas, and Information leaflets will be available for both patients and healthcare professionals at these sites (through the Antenatal Clinics, Antenatal Wards and Day Assessment Units). The direct care team will make the initial approach to potential participants, will provide interested women with a participant information sheet and take verbal consent to share their details with the research team. These women will then be consented and screened by the research team according to the criteria detailed above.

Eligible women who wish to participate in the study will be seen at a baseline visit in hospital following delivery. At this stage there will be formal confirmation of consent and randomisation will take place.

Women who suffer an adverse perinatal outcome (Special Care Baby Unit admission, intrauterine fetal death or neonatal death) will not be automatically excluded from the study, but there will be careful consultation with the midwifery and obstetric teams before these women are approached, and they will be handled sensitively.

7.2. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent Form (ICF) before any study specific procedures are performed (including screening). The original consent process and screening will take place prior to birth, and therefore there will be formal confirmation of consent at the baseline visit in hospital after delivery: Study procedures will be re-discussed, and a second copy of the participant information sheet provided if necessary. Confirmation of consent will be verbal, but will be documented in the participant's maternity records.

Written and verbal versions of the participant information and informed consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will have time between first approach and delivery of their baby to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. One copy of the signed informed consent will be given to the participant and one copy will be included in the participant's maternity records. The original signed form will be stored at the PCCTU (with participants' consent).

We will inform GPs and community midwives in writing of their patient's involvement in the study.

Patient experience qualitative sub-study: participants will consent to optional extended visits at 4 weeks and 26 weeks where structured interviews to assess their experience of self-management of blood pressure in the postpartum period will be conducted. Some baseline data will also be collected at the screening appointment.

Vascular risk sub-study: Women will consent to an optional extended visit at baseline and 12 weeks where measures of arterial stiffness and capillary density will be taken, and a fasting blood sample will be taken.

7.3. Visit 1: Screening and Eligibility Assessment

Screening (post consent) will involve collecting the demographics, age at entry to the study (years and months), weight at booking, height, BMI at booking, ethnicity, medical history, obstetric history, drug history and social history. We will ask women whether or not they are involved in any other medical research projects. Involvement in other research projects does not exclude women from this trial.

Personal data as follows will be collected and stored separately. This is to facilitate contact with participants during the study, and to arrange home follow-up visits (if participants agree):

- Forename and surname
- Address including postcode
- Medical record number (to allow access to patient's medical records)
- Telephone number

Details of the following aspects of the diagnosis of gestational hypertension / pre-eclampsia will be recorded:

- Blood pressure at booking
- Gestation at diagnosis of gestational hypertension or pre-eclampsia
- Gestation at which anti-hypertensive treatment was started
- Which anti-hypertensive drugs used
- What doses of anti-hypertensive drugs (and dose increases)
- Hospital admissions for gestational hypertension / pre-eclampsia
- Whether intravenous anti-hypertensive treatment was required
- Whether magnesium sulphate was required as eclampsia prophylaxis
- HDU or ICU care
- Significant proteinuria (record level)?
- Maternal complications of gestational hypertension / pre-eclampsia: renal dysfunction, HELLP syndrome, eclampsia, placental abruption
- Fetal complications of gestational hypertension / pre-eclampsia: in-utero growth restriction, placental insufficiency, intrauterine fetal death

Participants will be asked to complete the standardised Eq-5D-5L quality of life questionnaire at this visit.

7.4. Randomisation, blinding and code-breaking

A secure web-based randomisation system will be provided by the Oxford Primary Care Clinical Trials Unit. The system will allow for the allocation of patients to the two treatment groups: standard care or self-management on a 1:1 basis and for this allocation to be stratified according to recruitment site. Due to the nature of the intervention it will not be possible to blind patients, the recruiting clinician or data management staff within the clinical trials unit to the group allocation.

7.5. Visit 2: Baseline

The baseline visit will take place in hospital as soon as is practical after delivery (day 3, -2 or +3 days). There will be verbal confirmation of consent, and this will be documented in the participant's maternity notes.

Further baseline data will be collected at this visit:

- Days since delivery
- Date of delivery
- Mode of delivery
- *Any change from screening appointment?*
 - *Significant proteinuria (record level)?*
 - *Hospital admissions for gestational hypertension / pre-eclampsia*
 - *Number*
 - *Duration of each*
 - *Total duration*
 - *Whether intravenous anti-hypertensive treatment was required*
 - *Whether magnesium sulphate was required as eclampsia prophylaxis*

- *HDU or ICU care*
- *Maternal complications of gestational hypertension / pre-eclampsia:*
 - *Renal dysfunction (peak creatinine)*
 - *HELLP syndrome (peak alanine transaminase, lowest platelets, lowest haemoglobin, peak lactate dehydrogenase)*
 - *Disseminated intravascular coagulation*
 - *Neurological dysfunction: eclampsia, altered GCS, blindness, stroke, hyperreflexia + clonus, severe headache + hyperreflexia, persistent visual scotomata*
 - *Placental abruption*
- *Perinatal complications of gestational hypertension / pre-eclampsia:*
 - *In-utero growth restriction*
 - *Placental insufficiency i.e. abnormal dopplers*
 - *Premature delivery*
 - *Special Care Baby Unit admission (ICU, HDU or LDU) and length of stay*
 - *Intrauterine fetal death*
 - *Intrapartum stillbirth*
 - *Neonatal death*

We will measure participants left mid arm (or right if left cannot be used for blood pressure monitoring) in order to guide choice of blood pressure cuff size.

Participants will have their blood pressure checked after 5 minutes rest using the automated mode of a sphygmomanometer. 6 blood pressure readings will be taken at intervals of 1 minute. For the outcome measure of blood pressure control the mean of the second and third readings will be used. The mean of readings 2-6 will also be calculated as this has the potential to reduce the white coat effect. It may be anticipated that the intervention group may become more habituated to blood pressure monitoring, thereby reducing the white coat effect in this group. This approach attempts to reduce the potential bias that this habituation introduces.

Participants will be weighed at this visit using a standardised set of scales.

At each visit participants will be asked about:

- What anti-hypertensive medication they are currently taking
- Any side effects
- Any adverse events
- Concomitant medications

It is at this visit that participants will be randomised, and participants randomised to the intervention arm will be provided with a blood pressure self-monitor, and taught to use it. Prior to discharge from hospital participants in the intervention group will be given an individualised down titration schedule. This will be written by the research team in conjunction with the participant's direct care team.

If participants consent to participate in the vascular sub-study then this visit will be extended and will take place at the Cardiovascular Clinical Research Facility at the John Radcliffe Hospital, Oxford. A fasting blood sample (ideally 6 hours clear fluid only) will be taken to measure circulating biomarkers relevant to cardiovascular health, and three vascular assessments will be performed:

- Cardio-ankle vascular index (CAVI)
- Arterial tonometry
- Capillaroscopy

7.6. Visits 3-7: Follow-up

Participants will be followed up at 10 days, -2 or + 4 days (visit 3), 4 weeks +/- 1 week (visit 4), 6 weeks +/- 1 week (visit 5), 12 weeks +/- 1 week (visit 6) and 26 weeks +/- 2 weeks (visit 7) postpartum.

If women are discharged home after day 14 post-delivery (i.e. beyond the timing of visit 3), then an additional visit or telephone call will be arranged at the participant's convenience between discharge and visit 4 to ensure the participant's safety.

At each visit the participants will be seen by a member of the research team, and their eligibility and consent will be confirmed. At these visits, participants will have their blood pressure checked after 5 minutes rest using the automated mode of a sphygmomanometer. 6 blood pressure readings will be taken at intervals of 1 minute. For the outcome measure of blood pressure control the mean of the second and third readings will be used. The mean of readings 2-6 will also be calculated and recorded.

At each visit participants will be asked about:

- What anti-hypertensive medication they are currently taking
- Any side effects
- Any adverse events
- Concomitant medications

Visits 3, 4, and 7 will all be home visits or alternatively in the clinic or local general practice, at the woman's discretion. The visit at day 10 (visit 3) will aim to coincide with the routine community midwife appointment.

The visit at 6 weeks (visit 5) will be a clinic visit, and ideally will be scheduled alongside the routine postnatal check with the GP. If participants remain on anti-hypertensive treatment at this visit they will be offered referral to the specialist hypertension clinic for investigation for any underlying cause of secondary hypertension.

At visits 6 and 7 (12 and 26 weeks) participants will be weighed using a standardised set of scales.

At visits 5 and 7 (6 weeks and 26 weeks) participants will be asked to complete the EQ-5D-5L questionnaire.

If patients consent to participate in the vascular sub-study then visit 6 will take place at the Cardiovascular Clinical Research Facility at the John Radcliffe Hospital, Oxford. They will have the same vascular assessments performed as at baseline. If participants have not consented to participate in the vascular sub-study visit 6 will be at a participant's home.

If participants consent to participate in the qualitative patient experience sub-study then extended appointments at visits 4 and 7 will include structured patient experience interviews.

7.7. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may seek external review regarding discontinuing a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with study requirements*
- Loss of capacity to consent to involvement in research, for example due to developing puerperal psychosis
- Withdrawal of Consent
- Loss to follow up

*Non-compliance in either group would be defined as missing a trial visit, and not being contactable to reschedule the visit. Non-compliance in the intervention arm is defined as failing to report 3 consecutive blood pressure readings in the first 14 days after birth, or 5 consecutive blood pressure readings from this point onwards. The definition of 'significant non-compliance' necessitating withdrawal from the study will be an individualised judgement made by the research team in conjunction with a participant's direct care team. This judgement will be made on the basis of concerns regarding patient safety, and therefore will be influenced by the nature, frequency and clinical impact of a particular participant's non-compliance.

If a participant from the intervention arm withdraws from the study we will ensure that they return to usual blood pressure monitoring with their community midwife and GP. All participants will have their day 10 postnatal check with their midwife, and 6-week postnatal check with their GP as normal.

If a participant withdraws from the study their data will still be included in the data set unless they request their data be removed. As this is a trial-development pilot study withdrawn participants will not be replaced, as accurate assessment of the numbers of participants withdrawn and lost to follow is an important part of this study.

The reason for withdrawal will be recorded in the CRF if available.

7.8. Definition of End of Study

The end of study is the date of the last visit of the last participant.

8. INTERVENTIONS

8.1. Self-management of blood pressure

Participants in the usual care arm will have normal clinical care of their BP with their community midwife and GP. There will be no intervention in this group.

Participants in the intervention arm will be asked to perform daily BP readings at the same time each morning, at a time that is convenient to them: After 5 minutes rest they will perform two readings, more than 1 minute apart, and the second reading acted upon, in terms of how to adjust their medication. The self-monitoring BP data will be communicated centrally through the use of a smart phone app or text messaging based system. This service will respond to participants regarding the level of their BP and what action is required (if any). Participants in this group will be provided with an individualised medication adjustment schedule based on:

- Current treatment (which drugs, what doses)
- NICE guidance for management of hypertension in pregnancy (4):
 - If < 130/80 reduce / stop treatment
 - If < 140/90 consider reducing / stopping treatment
 - If $\geq$ 150/100 increase / start treatment
 - If $\geq$ 160/110 requires hospital review

The individualised medication adjustment schedules for each participant will be created by the research team in conjunction with the participant's usual care team. See Appendix D for standardised BP thresholds for medication adjustment (based on NICE guidance as above).

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

Participants will be advised to attend their local maternity unit for urgent review if blood pressure is $\geq$ 160/110 or they develop symptoms, which may be associated with hypertension (headache, visual disturbance, vomiting or upper abdominal pain). When on antihypertensive treatment, they will be advised to see their GP if their blood pressure is 150-159/100-109, or systolic < 100.

In the self-management arm we are withdrawing part of their usual blood pressure management by their GP and midwife. Therefore for safety it is important that participants in this arm adhere to the monitoring schedule. In the first 14 days after birth NICE recommends that BP is monitored on at least alternate days. Therefore if participants fail to report 3 consecutive blood pressure readings via the text message service or smart phone app, this will trigger the research team to contact them. From 14 days after delivery until treatment is discontinued, failure to report 5 consecutive blood pressure readings will trigger the research team to contact a participant.

9. SUB-STUDIES

9.1. Patient experience structured interviews

Additionally we will conduct structured interviews with participants in both arms who consent to participate in the qualitative sub-study to assess their experience of either usual care or self-management of blood pressure in the postnatal period, and to identify and explore factors related to the successful (or unsuccessful) implementation of the intervention. This embedded study will provide data regarding the views of patients as to the acceptability of self-monitoring in the routine management of gestational hypertension and pre-eclampsia after birth once they have been discharged from hospital.

Participants in both arms will be interviewed to explore barriers and facilitators to this self-management intervention at two stages during the trial. The control group will be interviewed to allow comparison of patient experience in the two arms.

Baseline data (5 questions) will be collected at visit 1 (screening). The structured interviews will be done at the 4 and 26 week visits (visits 4 and 7), and will take approximately 10-15 minutes on each occasion. There will be 5 questions for both groups, and an additional 5 questions in the intervention group.

An important focus of the interviews will be on identifying: perceived barriers; where similarities and differences in perception lie; appropriate behaviours and information sharing between patient, practitioner and practice staff necessary to maximise successful management; and patient satisfaction. We will use a structured interview approach with free text options, as this provides a reproducible format for consistency across interviews, while also allowing for further (free text) explanation. Structured responses will be entered on to a pre-coded scoring sheet. Free text responses will be audio-recorded and transcribed into Nvivo in order to capture all participant experiences.

At the interviews at screening and 4 weeks we will ask for the structured response first followed by any comments. At the final follow-up visit at 6 months we will aim to gather more detailed answers about participants' experiences so we will ask for their views followed by the structured response.

Structured, coded responses will be analysed using descriptive statistics (e.g. frequencies and cross-tabulations). Free text responses and interviewer notes will be analysed thematically. This dual approach will bring out both 'articulated' data i.e. direct responses to questions on the areas described above, as well as new 'emergent data'.

All women being enrolled into the trial will be asked if they consent to participate in this optional sub-study. All women who consent will be interviewed at visits 1 and 4. If more than 50 women (i.e. 25 from each group) consent to participate, then we will purposively sample these women to determine who undergoes the more detailed interview at the 6 month follow up visit. This sampling will be based on age, index of multiple deprivation, severity of hypertensive disorder of pregnancy (amount of medication at discharge from hospital, using WHO defined daily dosages) and in the intervention group adherence to self-monitoring.

9.2. Vascular risk

The following interventions will take place at baseline (visit 2) or day 10 (visit 3) and 12 weeks (visit 6):

- Cardio-ankle vascular index (CAVI) will be used to give a global assessment of arterial stiffness, independent of blood pressure. This involves placing blood pressure cuffs on both upper arms and ankles, with ECG monitoring and heart sound monitoring. Each measurement takes approximately 5 minutes.
- Radial arterial tonometry will be used to measure aortic blood pressure and augmentation index. This involves 3 lead ECG monitoring and using the SphygmoCor machine to analyse the radial arterial waveform. Each measurement takes approximately 10 minutes.
- Capillaroscopy will be used to study capillary density as a marker of microvascular changes related to hypertension. This involves using a microscope to look at the capillaries on the back of the finger at rest (functional capillary density) and with a pressure cuff inflated to 50mmHg (anatomical capillary density). Each measurement will take approximately 30 minutes.

- Investigators trained in venepuncture will take a 40ml fasting blood sample (ideally a minimum of 6 hours clear fluid only) to measure circulating biomarkers relevant to cardiovascular health. Venepuncture is considered necessary, as there is no other way that certain features of cardiovascular risk can be assessed. Lipid profile and glucose homeostasis (assessed by fasting insulin, glucose and HOMA) will be measured by standard techniques. Samples will also be used to measure routine inflammatory indices such as CRP and if considered appropriate novel proposed risk factors such as adhesion molecules, adipokines etc. Samples will be stored at -80°C in facilities within the Department of Cardiovascular Medicine. Measurements will be performed in batches, as appropriate, by laboratories in the University of Oxford, John Radcliffe Hospital or subcontracted laboratories under the direction of the investigators. With the explicit consent of participants for the gifting of samples, samples will then be transferred to a tissue bank for future use.

10. SAFETY

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

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

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

10.2. Expected Serious Adverse Events

The following SAEs (which must also fulfil at least one of the criteria listed in section 10.1) may be expected to occur in this patient population.

Potentially related to BP management	Unrelated to BP management
BP $\geq$ 160/110	Vaginal bleeding
BP < 90/50 whilst on treatment	Endometritis
Seizure	Sepsis
Intracranial haemorrhage	Pyelonephritis
Stroke	Mastitis
Faint	Surgical site infection
Fall	Paralytic ileus

Headache	Visceral injury (ureter, bladder, bowel)
Vomiting	Pelvic collection
Upper abdominal pain	Haematoma

10.3. Recording and Reporting Procedures for Adverse Events and Serious Adverse Events

Safety reporting will be from baseline to the 26 week follow up visit.

Adverse events may also be recorded by the participant using the trial telephone number, email, or via the text message service or smart phone app. Participants will be directly asked about adverse events at each study visit.

All serious adverse events, whether 'expected' (see table above in section 9.2.) or 'unexpected', need to be reported. All serious adverse event (SAE) information will be recorded on the PC-CTU SAE report form by the site or the CI and faxed to the Trials Unit's dedicated fax line, which is monitored during office hours. SAEs will be reported to the PC-CTU as soon as possible, preferably within 24 hours of the site becoming aware of the event. The PC-CTU will perform an initial check of the report, request any additional information from the reporting clinician and ensure that the CI or safety delegator reviews and evaluates the report for expectedness and relatedness. All SAE reports will also be reviewed routinely by the Data Monitoring and Ethics Committee, and all SAEs will be followed up until resolution or the end of the study period.

A SAE occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Related and unexpected SAEs will also be reported to the sponsor. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event.

11. LONE WORKING POLICY

As part of the trial follow up visits the research team will conduct home visits if this is acceptable to participants. These will be conducted in line with the University of Oxford Safety Office 'Safety in fieldwork' policy (UPS S5/07 <http://www.admin.ox.ac.uk/safety/policy-statements/s5-07/>).

12. STATISTICS AND ANALYSIS

12.1. Description of Statistical Methods

The analysis will be carried out on the basis of intention-to-treat (ITT). This is, after randomisation, participants will be analysed according to their allocated intervention group irrespective of what they actually receive. The analyses for this pilot study will be primarily descriptive and will not include any hypothesis testing or presentation of P-values for group comparisons.

Continuous variables will be reported as means with standard deviations (or medians with Interquartile ranges if skewed). Categorical variables will be reported as counts and percentages. Differences between

groups will be calculated and described with 95% confidence intervals only and will not include significance tests with P-values.

12.2. The Number of Participants

A formal sample size calculation is not required for this pilot study. We will aim to recruit 100 women (i.e. 50 women will be randomised to each arm).

12.3. Analysis of Outcome Measures

The primary objective is to assess feasibility issues. For this analysis, descriptive statistics will be calculated and assessed for each group.

Criteria for success of this pilot study:

- Recruitment rate:
 - Minimum of 3 participants recruited per week across all sites
 - No centre to contribute < 5% of study participants
- Attrition rate of < 10%
- Compliance rate > 90%
 - *Number of study visits attended by all participants / total number of intended study visits (n x 7)*

Potential outcomes for this pilot study:

- Stop – main study not feasible
- Continue, but modify protocol – feasible with modifications
- Continue without modifications but monitor closely – feasible with close monitoring
- Continue without modifications – feasible as is

Difference in blood pressure between groups, to inform the planned future main trial, will be estimated using a mixed effect model and described with 95% confidence intervals only. Further we will explore the validity of a 'time in range' measure as previously described in the analysis of the management of oral anticoagulant therapy by Rosendaal et al in 1993 (13).

A detailed statistical analysis plan will be written with our statistical team and will be completed before receipt of the data.

12.4. Interim analysis

There is no planned interim analysis for this study. All Serious Adverse Events reports will be reviewed by a Data Monitoring and Ethics Committee. This committee will meet annually or more if required, receiving reports in order to facilitate trial oversight and safety assessment. The trial team will be blinded to this data, and no statistical analysis will be conducted.

13. DATA MANAGEMENT

13.1. Access to Data

The delivery of the intervention will involve patient home visits. In order to facilitate these visits the study team will require access to patient identifiable data to include patient names, home addresses and telephone numbers. The consent form will clearly list the data to be collected and for what purpose. Only data required for this defined purpose will be collected and held by the research team. The identifiable data will be held securely at the Primary Care Clinical Trials Unit, University of Oxford, with access to this data restricted to appropriate members of the study team identified on the delegation log. Identifiable data will be held separately from other clinical data and anonymised as soon as no longer required in line with PC-CTU SOPs.

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

13.2. Data Recording and Record Keeping

All study data required for analysis will be recorded on paper Case Report Forms (CRFs) and returned to the study team for data entry. CRFs will be held securely in locked filing cabinets, located within office space with restricted entry. All data points will be transferred from paper CRFs to a secure database management system (CDMS) hosted by the PC-CTU. Within the CDMS patients will be identified solely by a unique study identification number. No patient identifiable data will be held within the CDMS. At the conclusion of the trial, following database lock and final analysis all documents will be appropriately archived for at least five years in line with PC-CTU standard operating procedures.

14. QUALITY ASSURANCE PROCEDURES

The CI will ensure the study is conducted in accordance with the current approved protocol, PC-CTU SOPs and all applicable local and national guidelines and regulations. The PC-CTU will conduct a study specific risk assessment prior to study commencement, which will inform the level and nature of monitoring required for this study.

A Trial Management Group (TMG) will be established to support the CI in overseeing the progress and conduct of the study.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Declaration of Helsinki

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

15.2. Guidelines for Good Clinical Practice

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

15.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

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

15.4. Reporting

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

15.5. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and CDMS. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so. All data generated from the text messaging service and smartphone app will all be anonymised prior to entry into the CDMS.

15.6. Expenses and Benefits

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

15.7. Other Ethical Considerations

In the self-management arm we are withdrawing part of participants' usual blood pressure management by their GP and midwife. Therefore for safety it is important that participants in this arm adhere to the monitoring schedule. In the first 14 days after birth NICE recommends that BP is monitored on at least alternate days. Therefore if participants fail to report 3 consecutive blood pressure readings via the text message service or smart phone app, this will trigger the research team to contact them. From 14 days after delivery until treatment is discontinued, failure to report 5 consecutive blood pressure readings will trigger the research team to contact a participant.

If women in the intervention arm still require additional support from the GP or community midwife postpartum for other medical, psychiatric or social issues then this will continue irrespective of their involvement in the trial. It will only be additional community midwife or GP input for blood pressure management alone that will be withdrawn.

Any incidental findings that arise as a result of study procedures or investigations (for example blood results) will be communicated directly to participants by the CI. With a participant's consent these findings will be passed on to the participant's GP so that appropriate follow up can be arranged if required.

16. FINANCE AND INSURANCE

16.1. Funding

This study is funded by NIHR Collaborations for Leadership in Applied Health Research and Care.

16.2. Insurance

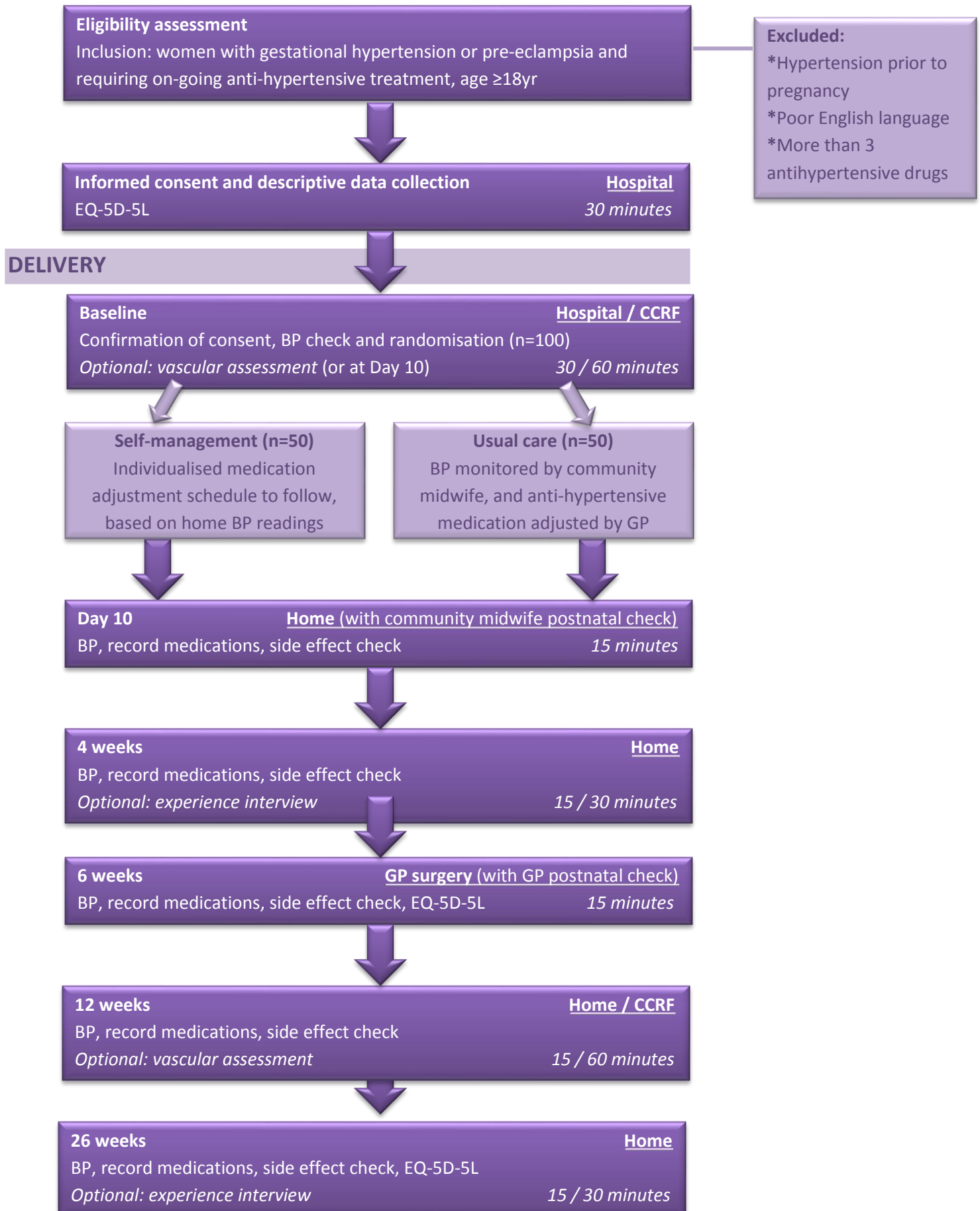
The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment, which is provided.

17. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by NIHR. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

18. REFERENCES

1. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. *BMJ*. 2013;347:f6564.
2. National Institute for Health and Care Excellence. NICE Clinical Guideline 107: Hypertension in pregnancy: Costing report. Implementing NICE guidance.; 2010.
3. Lazdam M, de la Horra A, Diesch J, Kenworthy Y, Davis E, Lewandowski AJ, et al. Unique blood pressure characteristics in mother and offspring after early onset preeclampsia. *Hypertension*. 2012;60(5):1338-45.
4. National Institute for Health and Care Excellence. NICE Clinical Guideline 107: Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. 2011.
5. McManus RJ, Mant J, Bray EP, Holder R, Jones MI, Greenfield S, et al. Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial. *Lancet*. 2010;376(9736):163-72.
6. McManus RJ, Mant J, Haque MS, Bray EP, Bryan S, Greenfield SM, et al. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical trial. *JAMA*. 2014;312(8):799-808.
7. Podymow T, August P. Postpartum course of gestational hypertension and preeclampsia. *Hypertens Pregnancy*. 2010;29(3):294-300.
8. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol*. 2010;10:1.
9. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract*. 2004;10(2):307-12.
10. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension*. 2009;53(6):944-51.
11. Paradisi G, Biaggi A, Savone R, Ianniello F, Tomei C, Caforio L, et al. Cardiovascular risk factors in healthy women with previous gestational hypertension. *J Clin Endocrinol Metab*. 2006;91(4):1233-8.
12. General Medical Council. 0-18 years: guidance for all doctors. 2007.
13. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost*. 1993;69(3):236-9.

19. APPENDIX A: STUDY FLOW CHART

20. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures	Visits (<i>all timings in relation to date of delivery</i>)						
	1: Screening	2: Baseline Day 3 - 2 or +3d	3: Day 10 - 2 or +4d	4: 4 weeks +/- 1w	5: 6 weeks +/- 1w	6: 12 weeks +/- 1w	7: 26 weeks +/- 2w
Informed consent	X						
Verbal confirmation of consent		X	X	X	X	X	
Demographics	X	X					
Medical history	X	X					
Eligibility assessment	X						
Eligibility confirmation		X	X	X	X	X	X
Randomisation		X					
Blood pressure check		X	X	X	X	X	X
Document medications	X	X	X	X	X	X	X
Side effect check		X	X	X	X	X	X
Adverse event assessment			X	X	X	X	X
Weight	Record booking weight	X				X	X
EQ-5D-5L	X				X		X
Offer specialist hypertension assessment if on-going treatment					X		
Structured patient experience interview (<i>optional</i>)	X			X			X
Vascular risk measurements (<i>optional</i>)		EITHER X	OR X			X	

21. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	4.0	19/01/2015	A Cairns	Participants will be weighed at visits 2, 6 and 7.
2	5.0	08/06/2016	A Cairns	• Vascular assessments to take place at baseline or day 10 visit • Windows for visits 2,3 and 4 adjusted • If participants discharged after day 14, additional visit or phone call will be arranged before 4 weeks at the participants' convenience • Serious adverse events: altered to make it clear that symptoms must also fulfil one of the criteria listed in section 10.1 in order to be classified as a serious adverse event Data analysis: No centre to contribute < 5% of study participants
3	5.1	16/06/2016	A Cairns	Protocol amended to reflect the title used in practice for our independent oversight committee from Independent Safety Review Committee to Data Monitoring and Ethics Committee and added a small amount of text to clarify the role of this committee in line with our trial's risk assessment.

22. APPENDIX D: Blood pressure thresholds for self-management**For women on anti-hypertensive treatment:**

Colour	Level	Blood pressure	Action
RED	VERY HIGH	SYS 160 or more OR DIA 110 or more OR Symptoms	Your blood pressure is very high. Sit quietly for 5 min and repeat blood pressure reading. If this is a repeat reading record a RED reading: Contact your local maternity unit immediately and arrange urgent assessment today.
ORANGE	HIGH	SYS 150-159 OR DIA 100-109	Your blood pressure is high. Sit quietly for 5 min and repeat blood pressure reading. If this is a repeat reading record an ORANGE reading: Contact your GP or midwife urgently and arrange assessment today.
YELLOW	RAISED	SYS 140-149 OR DIA 90-99	Your blood pressure is raised. Record a YELLOW reading. No change in your medication yet.
GREEN	HIGH NORMAL	SYS 130-139 OR DIA 80-89	Your blood pressure is in the target range when on treatment. Record a GREEN reading. This is fine provided that you have no side effects.
BLUE	LOW NORMAL	SYS 100-129 AND DIA less than 80	Your blood pressure is normal but you may require less treatment. Record a BLUE reading. Follow your medication change instructions if two days in a row in BLUE.
PURPLE	LOW	SYS less than 100 AND DIA less than 80	Your blood pressure is too low. Sit quietly for 5 min and repeat blood pressure reading. If this is a repeat reading record a PURPLE reading: Contact your GP or midwife urgently and arrange assessment today.

For women off anti-hypertensive treatment:

Colour	Level	Blood pressure	Action
RED	VERY HIGH	SYS 160 or more OR DIA 110 or more	Your blood pressure is very high. Sit quietly for 5 min and repeat blood pressure reading. If this is a repeat reading record a RED reading: Contact your local maternity assessment unit for urgent review today.
ORANGE	HIGH	SYS 140-159 OR DIA 90-109	Your blood pressure is high. Sit quietly for 5 min and repeat blood pressure reading. If this is a repeat reading record an ORANGE reading: If 2 or more consecutive readings in this range contact your GP or maternity assessment unit for review within 48 hours.
GREEN	NORMAL	SYS less than 140 AND DIA less than 90	Your blood pressure is normal. Record a GREEN reading.

APPENDIX 13: SNAP-HT Patient facing documents

- a. SNAP-HT advert
- b. SNAP-HT patient information sheet
- c. SNAP-HT informed consent form
- d. SNAP-HT GP/CMW letter (intervention group)
- e. SNAP-HT GP/CMW letter (control group)

Self-maNAgeMENT of Postnatal anti-Hypertensive Treatment

SNAP-HT Trial Development Pilot Study

Have you developed raised blood pressure requiring treatment in pregnancy?

We are carrying out a study to investigate the role of **self-management** of raised blood pressure after birth and are looking for women to participate.

If you are **pregnant** and have developed **newly raised blood pressure** (gestational hypertension *or* pre-eclampsia) which has **required drug treatment** then you are eligible for the study, provided you are:

- **Aged 18 or over**
- **Speak English**
- **Did not have high blood pressure prior to pregnancy**
- **Are taking no more than three different blood pressure medications**

The study involves blood pressure measurement and questionnaires and would be in addition to your usual antenatal and postnatal care.

CONTACT:

Dr Alexandra Cairns (Study Co-ordinator)

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<<insert trust
logo>>

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Self-maNAgeMent of Postnatal anti-Hypertensive Treatment: SNAP-HT Trial Development Pilot Study



Participant Information Sheet

Information about a study you are invited to join

We would like to invite you to take part in a research study. Joining the study is entirely up to you. This information sheet explains why the research is being conducted and what it would involve if you did decide to take part. If you have any questions, please do not hesitate to ask.

Please feel free to talk to others about the study.

Summary of the study

- ❖ **Raised blood pressure** is **common** in pregnancy (affecting approximately 1 in 10 women)
- ❖ Blood pressure **remains elevated after birth**, but usually **returns to normal over 2 – 12 weeks**
- ❖ We want to assess **how best to monitor blood pressure**, and **manage the treatment** of raised blood pressure during this period
- ❖ We want to know whether the use of **home blood pressure monitors** can assist with this
- ❖ To try to answer this question we plan to **randomly allocate** women to either **usual care** of their blood pressure after birth of their baby (with their GP and midwife) or to **self-management** of blood pressure
- ❖ The **main purpose** of this study is to **assist with the planning** of a **large-scale trial**
- ❖ The study **follow-up period is 6 months**, and will involve **7 visits** in total. The majority of these visits will be home visits, or alongside routine appointments with your GP or midwife
- ❖ There are two **optional** sub-studies:
 - Assessing markers of the long term risk of developing heart or other disease affecting the blood vessels
 - Assessing patient experiences of both usual care and the self-management approach

**If you think you might be interested in participating in the study then please
continue reading for more details.**

What is the purpose of this study?

Raised blood pressure is common in pregnancy, affecting about one in ten women. For some of these women, raised blood pressure is an indication of pre-eclampsia: this is a condition that usually affects women during the second half of pregnancy or immediately after delivery of their baby. Pre-eclampsia is defined as newly arising high blood pressure combined with protein leaking into the urine. After pregnancy, women's blood pressure generally remains elevated for a period of time and in most cases gradually returns to normal. Therefore during this period (normally between 2 and 12 weeks) medication will need to be gradually adjusted to achieve the correct blood pressure control.

We would like to find out whether regular blood pressure measurement by women themselves during this period, and adjustment of medications according to an individualised schedule, could improve blood pressure control and patient satisfaction.

This study is a pilot study: it has been set up in order to inform the planning of a large-scale multi-centre randomised controlled trial by testing the feasibility of methods and procedures for later use on a large scale. We want to increase our experience of applying this management approach in this subset of patients; to look for possible effects of this intervention; to assess recruitment potential; and to evaluate feasibility of coordinating this trial across several centres. The primary objective of the large-scale trial will be to determine whether self-management can improve blood pressure control in women with raised blood pressure during the period after birth.

100 women will be recruited to the study, and will be randomly assigned to one of two groups in order to allow us to compare self-management of blood pressure with usual care.

Why have I been invited?

You have developed raised blood pressure requiring treatment during your pregnancy. This may be a diagnosis of gestational hypertension (raised blood pressure without a significant leak of protein into your urine), or pre-eclampsia (raised blood pressure in association with a significant leak of protein into your urine).

What will happen to me if I take part?

If you decide you would like to take part, we will arrange a screening appointment before you give birth, either within your GP surgery or alongside hospital appointments if you prefer. You will sign a consent form and will complete a short questionnaire including questions about your medical history, pregnancy, what medicines you take and asking you about your day-to-day life. This questionnaire should not take you more than 10 minutes to complete.

After birth we will arrange your first visit whilst you remain in hospital. At this visit we will verbally confirm that you continue to consent to participate in the trial, and you will have the option to withdraw. We will measure your blood pressure and randomly allocate you to one of the groups, either usual care or self-management of blood pressure.

If you are allocated to the **usual care** group you will have your blood pressure monitored by your community midwife and GP once you have been discharged from hospital. The frequency of this monitoring will be decided by your Obstetric team. Your GP will adjust your blood pressure medication according to the readings that they and your midwife obtain.

If you are allocated to the **self-management** group we will provide you with a home blood pressure monitor and show you how to use it. You will be asked to measure your blood pressure at the same time each morning after you leave hospital and record the readings in a booklet. You will be given an individualised schedule for gradually decreasing your medication(s), which you will follow on the basis of your own blood pressure readings. Once you have stopped your blood pressure medication we will ask you to check your blood pressure three times weekly for one week, and provided it remains normal to then check it once weekly for the remainder of the trial follow up period (6 months).

We will arrange appointments to see you and measure your blood pressure and go through short questionnaires at 10 days, 4 and 6 weeks, 3 and 6 months after birth: see study flow chart (page 6). At the first visit after birth, and at the 3 and 6 month follow up visits we will weigh you.

Are there any optional components to the research study?

Yes there are **two optional sub-studies** that are part of this research study, which are designed to investigate the long-term risk of developing raised blood pressure and heart disease, and to examine participants' health experiences. These are called the vascular risk and patient experience sub-studies.

What is involved in the 'vascular risk' sub-study?

This study is to examine the effect of raised blood pressure in pregnancy and after delivery on women's **long-term risk of developing raised blood pressure and heart disease**. We want to look at how different measures change between birth and 3 months after birth, and want to see if this change is different in the two groups (self-management and usual care). This will help us to assess whether improving the control of blood pressure after birth can modify women's risk of developing health problems in the future.

Participation in this sub-study is optional, and will involve extended appointments at either the baseline visit or the day 10 visit and 3 month follow up visits. These appointments will last about an hour and will take place at the Cardiovascular Clinical Research Facility (CCRF) at the John Radcliffe Hospital, Oxford. Your travel and parking expenses will be paid, and a midwife or other healthcare professional will be available to look after your baby. At each appointment the following additional tests will be performed to look at different markers of vascular risk:

- A fasting, 40ml blood sample (equivalent to 7 teaspoons) will be taken (ideally after 6 hours only drinking clear fluids);
- Measurement of your blood pressure in both your arms and your ankles together with monitoring of your pulse, and takes about 5 minutes;

- Measurement of blood pressure in a different form, which involves a mini heart tracing / ECG (3-leads attached to your chest) and using a small probe to scan the pulse at your wrist. This takes approximately 10 minutes;
- We will use a microscope to look directly at the density of small blood vessels (capillaries) on the back of the finger at rest and with a small cuff inflated around your finger. Each measurement will take approximately 30 minutes.

We anticipate these tests will only cause minor discomfort and they are not associated with any long term adverse effects. If any abnormal results are found as part of this study we will notify you in person and will explain what they mean.

With your express consent these results will be passed on to your GP so that appropriate follow up and management can be arranged.

With your explicit consent, once the blood samples have been analysed, they will be transferred for storage in a 'research tissue bank' so that they can be used for future research.

What is involved in the 'patient experience' sub-study?

This voluntary study aims to understand **participants' experiences** from using a self-management approach in the care of raised blood pressure after pregnancy, when compared to participants' experiences when undergoing usual care.

All participants who consent to participate in this sub-study will be asked five questions at the screening appointment. These questions will focus on how well informed you feel about your diagnosis of raised blood pressure in pregnancy, and how in control you feel of your treatment.

For participants in the 'usual care' group these five questions will be repeated at the 4 week and 6 month follow up visits.

For participants in the 'self-management' group these five questions, plus an additional five (ten in total) will be repeated at the 4 week and 6 month follow up visits. We anticipate this will add about 10-15 minutes to each visit. On the last visit we will aim to gather more detailed answers to these questions which may take around 30 minutes. The additional questions aim to explore participants' experience of the self-management approach, and whether this is a management approach they would recommend to others or wish to use themselves in the future.

Answers to questions will be audio recorded as well as written down. Your name will not be on the tape and we will remove your name from the interview transcripts to keep your identity confidential. Direct quotes may be used in publications but these will be numbered and anything which could identify you will be removed. Nothing that you say will be fed back to the doctors and nurses involved in your care as coming from you.

How do I monitor my blood pressure at home (intervention group only)?

You will be provided with a blood pressure monitor that is suitable and accurate in pregnancy and after birth. You will be asked to use the monitor once a day, at the same time each morning, whenever is convenient. You will be given a simple blood pressure diary to complete.

You will be asked to use a text based system or smart phone app on a daily basis that allows results to be communicated to a central server.

What will happen if I have very high or low readings?

You will be given clear instructions about what to do and who to call if consistently high or low blood pressure readings are obtained.

Do I have to take part?

No, this is a voluntary study, and it is your decision to participate. If you decide not to take part, or if you agree but later change your mind, you will still receive the same standard of medical care. You are free to withdraw from the study at any time without giving a reason. We will contact your GP to inform them that you are no longer participating in the study, so that any ongoing care you require is reinstated if necessary.

What are the possible benefits or disadvantages of taking part?

The main aim of this study is to assess the feasibility of carrying out a larger study, which will then lead to improved health care. We hope that information from this work will improve the care of women with raised blood pressure after birth, possibly reducing the length of stay in hospital, the number of readmissions to hospital with inadequately controlled blood pressure, and potentially the number of appointments to see your GP. We also hope that achieving better blood pressure control in the period after birth may contribute to better long-term health outcomes.

Other than the time taken to undertake the study we do not anticipate any other disadvantage from taking part.

Will my expenses be paid?

Most appointments will be either in hospital, or alongside your usual midwife or GP appointments at no additional expense to yourself, or we will arrange to see you at home if this is convenient for you. If you need to travel to any appointments or consent to attend the extended follow up visit at 3 months at the CCRF based at the John Radcliffe Hospital in Oxford then your travel expenses will be reimbursed.

We anticipate that the text messaging service will use free text messages, and that the smartphone app will only require a small amount of data usage. If you find that this is not the case, and that these services are costing you money, please let us know and we will reimburse you.

Will my taking part in this study be kept confidential?

All of the information collected will be made anonymous. During the study the research team may need to access relevant sections of your medical notes. This and the information that you provide will be coded with a study number so you cannot be identified from it. At the end of

the study we will seek your permission to retain your contact details and to contact you for any follow-up studies (*optional*).

During the study follow up period we will keep contact details for you (name, address, telephone number and medical record number) to facilitate contact with you. These will be kept separately to the remainder of the research data and will be anonymised once the study follow up is complete. This data, together with the consent form you will have signed, will be stored at the Primary Care Clinical Trials Unit, University of Oxford. The research team have a duty of confidentiality to you as a research participant. All data will be kept securely according to the Data Protection Act 1998. Responsible members of the University of Oxford or the NHS Trust may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations. Your GP and midwife will be informed that you are taking part in this study and a note will be placed in your postnatal folder and maternity records to inform other health professionals involved in your postnatal care.

What will happen if I don't want to carry on with the study?

If you decide you no longer wish to take part in our study, you can phone, write to or e-mail the study co-ordinator. You can withdraw from the study at any time without giving a reason. Should you wish to withdraw, please let us know if we can keep the information we have collected about you so far or if you would prefer it to be destroyed? Please also return the blood pressure monitor to your GP practice.

What if there are any problems?

If you have any queries about the study, please contact the study co-ordinator (Alexandra Cairns). If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, please contact Alexandra Cairns, or you may contact the University of Oxford Clinical Trials and Research Governance office (see below for contact details). Alternatively you may wish to contact your hospital's Patient Advice and Liaison Service (PALS: see below for contact details).

The University of Oxford has arrangements in place to provide for harm arising from participation in the study for which the University is the Research Sponsor. NHS indemnity operates in respect of the clinical treatment with which you are provided.

What will happen to the results of the study?

The summarised results will be published in a scientific journal/s and summarised on our website (<http://www.primarycare.ox.ac.uk/>) for you to read.

Who is organising and funding the research?

The study is being run by **Dr Alexandra Cairns** (Clinical Fellow, Nuffield Department of Primary Care Health Sciences) as part of her doctoral studies at the University of Oxford, and supervised by **Professor Richard McManus** (Nuffield Department of Primary Care Health Sciences, University of Oxford), **Professor Paul Leeson** (Cardiovascular Clinical Research Facility, University of Oxford) and **Dr Lucy Mackillop** (Consultant Obstetric Physician, Oxford University

Hospitals NHS Trust). Study visits will be conducted by either Alexandra Cairns or Carole Crawford (Research Midwife).

The research is being financed by the National Institute for Health Research through the Collaboration for Leadership in Applied Health Research and through Fellowship Funding for Dr Cairns. The sponsor of the study is the University of Oxford.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This study has been reviewed by South-Central Oxford C (reference 14/SC/1316).

Do I have to decide at once?

No. As we aim to first contact you before delivery, you can take time to think about it. Participants will need to consent to participate prior to delivery and are eligible to begin participating in this study immediately following delivery.

What happens now?

If you are interested in taking part please let us know and we will arrange your screening and baseline appointments.

Study contact details

CONTACT DETAILS

Chief Investigator: Dr Alexandra Cairns

Nuffield Department of Primary Care Health Sciences, University of Oxford

Radcliffe Observatory Quarter, Woodstock Road, Oxford OX2 6GG

alexandra.cairns@phc.ox.ac.uk

0800 9150045

Local Principal Investigator: *insert local details*

insert local details

Clinical Trials and Research Governance: Heather House

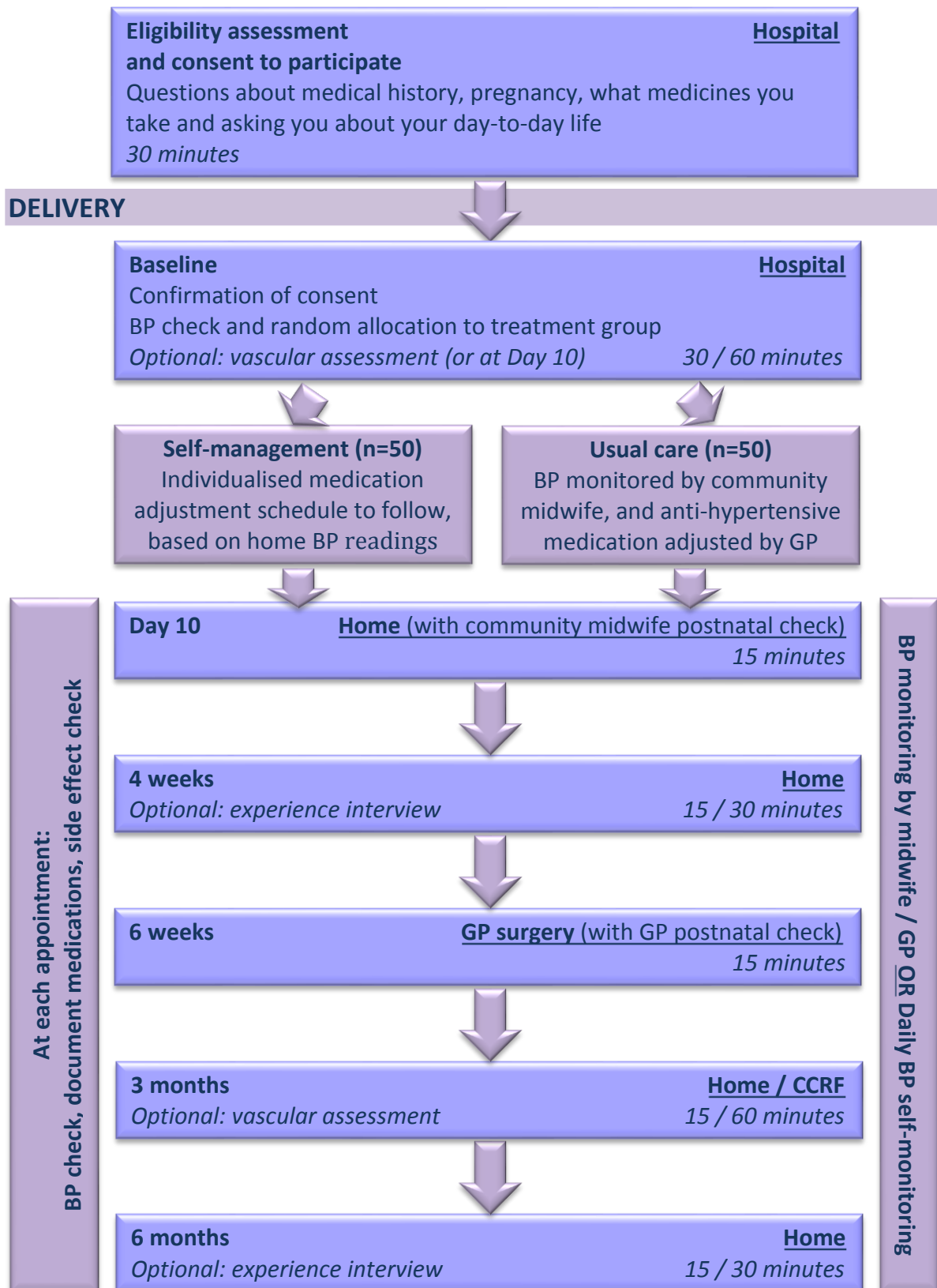
heather.house@admin.ox.ac.uk

01865 572224

Patient Advice and Liaison Service (PALS):

insert local details

Study flowchart



Self-management of postnatal anti-hypertensive treatment SNAP-HT trial-development pilot study

INFORMED CONSENT FORM: MAIN STUDY

ID Number: SNAP - __ - __ - __

Please initial:

1. I confirm that I have read and understood the information sheet dated 19/01/2015 version 3.0 for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily. ☐
2. I understand that my name, medical record number and contact details will be held separately from trial data for the duration of the study. This data will be stored with this consent form at the Primary Care Clinical Trials Unit, University of Oxford. ☐
3. I understand that data collected during the study will be held securely at the University of Oxford, Department of Primary Health Care Sciences. ☐
4. I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
5. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Oxford, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
6. I consent to my GP and any other health care professionals involved in my postnatal care being made aware of my participation in this study. ☐
7. I agree to participate in this study. ☐
8. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. ☐
9. I give my consent for my name and contact details to be retained and am happy to be contacted about future research (*optional*). ☐

Name of patient (printed)

Date

Signature

Name of person taking consent (printed)

Date

Signature

Self-management of postnatal anti-hypertensive treatment SNAP-HT trial-development pilot study

INFORMED CONSENT FORM: SUB-STUDIES

ID Number: SNAP - _ _ - _ _ _

Please initial:

VASCULAR RISK SUB-STUDY

1. I agree to take part in the vascular risk sub-study, involving extended appointments at baseline and 3 months (*optional*). ☐
2. I consider samples taken as part of the vascular risk sub-study a gift to the University of Oxford and I understand I will not gain any direct personal benefit from this (*optional*). ☐

QUALITATIVE PATIENT EXPERIENCE SUB-STUDY

3. I agree to take part in the qualitative patient experience sub-study involving extended appointments at 4 weeks and 6 months (*optional*). ☐
4. I understand that the interviews will be audio recorded but that I can refuse to answer a question if I wish and stop the interview at any time without having to give an explanation. ☐
5. I understand that the interview will be typed up and that the conversations in that interview may be used when the research team write about the study. However, any quotes will be anonymised and no information will be used in any presentations or reports that could lead to my identification. ☐

Name of patient (printed)

Date

Signature

Name of person taking consent (printed)

Date

Signature

Self-management of postnatal anti-hypertensive treatment SNAP-HT trial-development pilot study

__/__/201__

GP Surgery: _____

Dear _____,

This is to inform you that _____ is taking part in a clinical trial entitled 'Self-management of postnatal anti-hypertensive treatment: SNAP-HT trial development pilot study'. This is an un-blinded randomised controlled trial. Women who have developed gestational hypertension or pre-eclampsia requiring ongoing anti-hypertensive treatment in the postnatal period are recruited and then randomised to either usual care or self-management.

_____ has been selected because she has developed gestational hypertension / pre-eclampsia (*delete as appropriate*) in pregnancy and has been discharged from hospital on:

1.	Dose:	Frequency:	Route:
2.	Dose:	Frequency:	Route:
3.	Dose:	Frequency:	Route:

She has been randomised to **self-management**. Women in the self-management arm will be asked to monitor their BP daily, and adjust their medication according to an individualised down-titration schedule. They will be trained how to do this, given a monitor and instructions on contacting their GP or midwife should their BP be greater than 150/100 mmHg, or less than 100 systolic. These readings will replace those additional measurements normally performed by her community midwife. If they need to adjust their medication in a way which requires a different dose then we will ask them to contact you to arrange a prescription. We will provide you with a copy of their down titration schedule.

_____ will have additional appointments **with the research team** at day 10, then 4, 6, 12 and 26 weeks postpartum. We will endeavour to schedule the appointment at day 10 alongside her postnatal check with her community midwife. At 6 weeks we will try to schedule the appointment alongside her **routine** postnatal check with you. We would be very grateful if we could arrange to see her at your surgery, and will contact you to arrange this, if convenient for both you and her. The remainder of the appointments will be home visits. **All additional appointments will be undertaken by the research team and will not involve additional GP time.**

Self-management of postnatal anti-hypertensive treatment SNAP-HT trial-development pilot study

It is possible that you may be contacted by _____ if her home readings are very high or very low. Should this happen you are asked to check the blood pressure yourself and to follow your usual guidelines based on your own readings. If you require any advice about blood pressure monitoring and management in study participants then please do not hesitate to contact us.

A summary of the study and a flow chart is enclosed. Please do not hesitate to contact us for further information if required.

Many thanks,



Dr Alexandra Cairns

Clinical Fellow to Professor Richard McManus

Specialty Trainee in Obstetrics and Gynaecology

alexandra.cairns@phc.ox.ac.uk

Telephone: 0800 9150045

<< COPY OF STUDY FLOWCHART INCLUDED (as in participant information sheet) >>

Self-management of postnatal anti-hypertensive treatment SNAP-HT trial-development pilot study

__/__/201__

GP Surgery: _____

Dear _____,

This is to inform you that _____ is taking part in a clinical trial entitled 'Self-management of postnatal anti-hypertensive treatment: SNAP-HT trial development pilot study'. This is an un-blinded randomised controlled trial. Women who have developed gestational hypertension or pre-eclampsia requiring ongoing anti-hypertensive treatment in the postnatal period are recruited and then randomised to either usual care or self-management. _____ has been selected because she has developed gestational hypertension / pre-eclampsia (*delete as appropriate*) in pregnancy and has been discharged from hospital on:

1.	Dose:	Frequency:	Route:
2.	Dose:	Frequency:	Route:
3.	Dose:	Frequency:	Route:

She has been randomised to **usual care**. Women in the usual care arm will undergo their normal postnatal follow up with their community midwife and GP, and have their blood pressure and anti-hypertensive medication managed in the normal way, guided by any advice from their obstetric team.

_____ will have additional appointments **with the research team** at day 10, then 4, 6, 12 and 26 weeks postpartum. We will endeavour to schedule the appointment at day 10 alongside her postnatal check with her community midwife. At 6 weeks we will try to schedule the appointment alongside her **routine** postnatal check with you. We would be very grateful if we could arrange to see her at your surgery, and will contact you to arrange this, if convenient for both you and her. The remainder of the appointments will be home visits. **All additional appointments will be undertaken by the research team and will not involve additional GP time.**

Self-management of postnatal anti-hypertensive treatment SNAP-HT trial-development pilot study

If you require any advice about blood pressure monitoring and management in study participants then please do not hesitate to contact us. A summary of the study and a flow chart is enclosed. Please do not hesitate to contact us for further information if required.

Many thanks,



Dr Alexandra Cairns

Clinical Fellow to Professor Richard McManus

Specialty Trainee in Obstetrics and Gynaecology

alexandra.cairns@phc.ox.ac.uk Telephone: 0800 9150045

<< COPY OF STUDY FLOWCHART INCLUDED (as in participant information sheet) >>

APPENDIX 14: SNAP-HT Statistical analysis plan

STATISTICAL ANALYSIS PLAN

Self-management of postnatal antihypertensive treatment: a trial development pilot study

	NAME	TITLE	SIGNATURE	DATE
Written by:	Alexandra Cairns	Chief Investigator		
Reviewed by:	Jill Mollison	Trial Statistician		
Approved by:	Ly-Mee Yu	Senior Trial Statistician		

Version History

Version:	Version Date:	Changes:
1.0	14/12/2016	Original

1 TABLE OF CONTENTS

1	Table of Contents.....	2
2	Introduction.....	4
2.1	Preface	4
2.2	Purpose and scope of the plan	4
2.3	Trial overview.....	5
2.4	Objectives.....	5
3	Trial design.....	6
3.1	Outcome measures.....	7
3.1.1	Primary outcome	7
3.1.2	Secondary outcomes.....	8
3.1.3	Exploratory analysis	11
3.2	Target population	11
3.3	Sample size.....	11
3.4	Randomisation and blinding in the analysis stage.....	12
4	Analysis – General considerations	12
4.1	Descriptive statistics	12
4.2	Characteristics of participants	12
4.3	Definition of population for analysis.....	13
4.4	Pooling of investigational sites	13
4.5	Data Monitoring Committee And Interim Analyses	13
5	PRIMARY ANALYSIS.....	15
5.1	Primary outcome	15
5.2	Handling missing data	16
5.3	Handling outliers.....	16
6	SECONDARY ANALYSIS.....	16
6.1	Secondary outcomes.....	16
6.1.1	Binary outcomes	16
6.1.2	Repeated measures outcomes	16
6.1.3	Continuous outcomes	17
6.1.4	Time to event outcomes	17
6.1.5	Count outcomes.....	17

6.1.6	Grouped binary outcomes	18
7	SUBGROUP ANALYSES	18
8	ADDITIONAL ANALYSES.....	18
8.1	Primary outcome	18
8.2	Completion of intervention	18
8.3	Secondary outcomes.....	18
8.4	Exploratory analyses	18
9	SAFETY ANALYSIS.....	19
9.1	Adverse events.....	20
10	QUALITY ASSURANCE.....	20
11	CHANGES TO THE PROTOCOL OR PREVIOUS VERSIONS OF SAP	21
12	References	22
13	Appendices.....	23
13.1	Appendix I. Schedule of procedures	23
13.2	Appendix II. Outcome assessment schedule	24
13.3	Appendix III. Consort flow diagram of trial participants.....	25

2 INTRODUCTION

2.1 PREFACE

Trial Statisticians: Ly-Mee Yu, Nicola Williams, Sena Jawad

Chief Investigator: Alexandra E Cairns

Supervisor: Richard McManus

Trial Manager: Emma Ogburn

Data Managers: Judi Read, Christopher Lovekin, Brendan Bradley

Protocol:

Study Title: Self-management of postnatal antihypertensive treatment: a trial development pilot study

Internal Reference Number / Short title: SNAP-HT trial development pilot study

Ethics Ref: 14/SC/1316

ClinicalTrials.gov Identifier: NCT02333240

Date and Version No: 08/06/2015 V5.0

2.2 PURPOSE AND SCOPE OF THE PLAN

This statistical analysis plan (SAP) will cover the main statistical analysis as stated in the protocol. The SAP will be agreed by the Trial Management Group (TMG) and Data Monitoring and Ethics Committee (DMEC), and signed off by the Chief Investigator (CI) and statisticians prior to database lock and data analysis. During any interim analysis the trial team will be blinded to participant allocation.

This document details the proposed presentation and analysis for the main paper(s) reporting results of the SNAP-HT trial. 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 analyses (for e.g. to decide cut off points for categorisation of continuous variables), nor to prohibit accepted practices (e.g. 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.

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 statistical analysis will be carried out by the Chief Investigator, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures. The analysis will be validated by an independent statistician at the Primary Care Clinical Trials Unit.

The ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials E9 (5 February 1998) was reviewed in order to complete this SAP.

2.3 TRIAL OVERVIEW

New-onset raised blood pressure (BP) affects about one in ten pregnancies. For some women, raised BP is an indication of pre-eclampsia: newly arising high BP in pregnancy combined with protein leaking into the urine. After birth, women's BP remains elevated for a period of time, but in most cases returns to normal over 2–12 weeks (1). During this period medication needs to be adjusted to achieve the correct control. Research suggests that severity of hypertension during this period is associated with adverse long-term health outcomes (2). We would like to find out whether home BP monitoring, and self-adjustment of medications according to an individualised protocol, could improve BP control and patient satisfaction.

This pilot study has been set up to inform the planning of a large-scale multi-centre randomised controlled trial by testing the feasibility of the protocol. We want to increase our experience of applying this management approach in this subset of patients; to select the most appropriate primary outcome measure and to estimate the effect size of this intervention; to assess recruitment potential; and to evaluate feasibility of coordinating this trial across several centres. The primary objective of the large-scale trial will be to determine whether the self-management approach can improve BP control in women with medicated hypertensive disorders of pregnancy (HDP) in the postnatal period.

Women recruited to the study will be randomly assigned to one of two groups: self-management or usual care. Participants allocated to 'usual care' will have their BP monitored and medication adjusted by their GP and midwife as normal. Participants allocated to the 'self-management' group will use a home BP monitor daily following discharge from hospital after birth. They will be provided with an individualised schedule for gradually decreasing their medication(s) in line with their BP readings. Women will be followed up for 6 months.

2.4 OBJECTIVES

Primary Objective

- Feasibility of study

Secondary Objectives

- To investigate whether self-management of hypertension in the postpartum period leads to improved blood pressure control

- To assess whether self-management of blood pressure in the postpartum period can reduce postnatal readmissions to hospital with poorly controlled hypertension.
- To assess patient experience of self-management of blood pressure in the postpartum period
- To determine whether better blood pressure control correlates with improved vascular risk markers
- Safety

Exploratory analysis

- To explore percentage time spent in range as a marker for blood pressure control in this setting
- Setting BP thresholds for future trials

3 TRIAL DESIGN

Multi-centre, non-blinded, randomised controlled trial. All results will be analysed on an intention to treat basis. The planned sample size is 100.

Trial arms:

- **Intervention** (Self-management of blood pressure): women randomised to self-management of blood pressure will have an individualised medication adjustment schedule based on NICE guidance for medication adjustment postpartum. They will be provided with, and taught to use, a home blood pressure monitor validated in pregnancy (Microlife WatchBP® Home) (3), and perform daily blood pressure readings until they have discontinued treatment. When treatment is discontinued we will ask them to continue daily blood pressure measurements for one week, and provided these are normal (<140/90) they will then be asked to check their blood pressure weekly for the remainder of the trial period. The self-monitoring BP data will be collated centrally through the use of a smart phone app or text messaging based system. This service will respond to participants regarding the level of their BP and what action is required. At the end of the study period the data from the home BP monitors will also be uploaded to the trial database. These blood pressure readings will replace those that would normally be taken by their community midwives. If women still require additional support from the GP or community midwife postpartum for other medical, psychiatric or social issues then this will continue.
- **Control** (usual care): women will have their blood pressure monitored by their community midwife, and will have their antihypertensive medication adjusted by their general practitioner.

Patient population: Women aged 18 years and over with gestational hypertension or pre-eclampsia requiring on-going antihypertensive medication in the postpartum period.

Study sites: Women undergoing obstetric care at the John Radcliffe Hospital (Oxford), Horton General Hospital (Banbury), Royal Berkshire Hospital (Reading), Stoke Mandeville Hospital (Aylesbury) and Northampton General Hospital (Northampton) will be approached during pregnancy.

Study period: Recruitment will occur for a 13-month period from April 2015. Women will be consented and screened during the antenatal period. They will be randomised shortly after birth, and commence the intervention after discharge from hospital postpartum. The intervention will continue whilst they remain on antihypertensive treatment. They will be followed up for 6 months.

Follow-up (see Appendix I. Schedule of procedures): After birth participants will be reviewed at a baseline visit whilst they remain in hospital (~day 3), and at this stage will be randomised (using a web-based randomisation system, stratified by site). They will have their blood pressure measured at this visit using an automated blood pressure monitor: 6 readings will be taken at 1 minute intervals.

All women will be followed up at 10 days, then 4, 6, 12 and 26 weeks postpartum and have their blood pressure measured by one of the study team. If women still require antihypertensive treatment at 6 weeks postpartum, they will be reminded to ask their GP about referral to the specialist hypertension clinic.

At the baseline visit, and 12 and 26 week follow up women will be weighed using a standardised set of scales. This is in order to evaluate whether the extent and speed of return to booking weight (a mark of pre-pregnancy weight) correlates with resolution of gestational hypertension.

Women from each group will be asked to complete the EQ-5D-5L Health Questionnaire to assess their quality of life at screening (visit 1), 6 weeks (visit 5) and 26 weeks (visit 7). Additionally we will conduct optional structured interviews with women from both groups in order to assess their experience of management of blood pressure in the postpartum period. Some baseline data will be collected at visit 1 (screening), and structured interviews will be done at the 4 (visit 4) and 26 week (visit 7) visits. We aim to recruit a minimum of 50% of participants in each group (i.e. 50 women, 25 from each group) into this sub-study.

We are planning a sub-study to analyse markers of vascular risk in women from both groups. Women will consent to an optional extended visit at baseline and 12 weeks where measures of arterial stiffness and capillary density will be taken. Additionally in women who consent to participating in this element of the study we will take a blood sample to measure circulating biomarkers relevant to cardiovascular health. We aim to recruit a minimum of 15 women from each group into this sub-study.

3.1 OUTCOME MEASURES

3.1.1 PRIMARY OUTCOME

All measured at the end of the trial period (see section 5.1).

- Recruitment rate is defined as the percentage of participants who were approached that were randomised. We will also calculate the percentage of eligible participants recruited.

We will also calculate the consent rate (percentage of participants who were approached that consented to inclusion in the study at the screening visit) and the conversion rate (percentage of participants who consented that were randomised).

- Retention rate is defined as the percentage of participants who were randomised who completed follow-up to 6 months (end of the trial), and also who completed follow-up to 6 weeks.
- Compliance rate is defined as the percentage of intended study follow-up visits (3 – 7) attended. We will also calculate the percentage of intended study follow-up visits (3 – 7) attended within the pre-defined time windows. These definitions have been amended slightly following publication of the study protocol, to remove the screening and baseline visits from the calculation. This was altered after discussion with the Trial Management Group (15 July 2016) and prior to any data analysis, because the original plan was confounded by changes in the study population between screening and baseline due to pre-randomisation withdrawals. Additionally, by definition all recruited participants will undergo a screening visit and all randomised participants will undergo a baseline visit: therefore including these visits in the calculations seems counterintuitive.

3.1.2 SECONDARY OUTCOMES

The trial is not powered for any of the secondary outcome measures or exploratory analyses (see also sections 6 and 8).

3.1.2.1 BLOOD PRESSURE CONTROL

A range of different outcomes will be analysed to explore how to best measure the concept of blood pressure control in the postnatal period, where both too high and too low blood pressure can have adverse consequences:

- Systolic blood pressure at each of trial visits 3 – 7 (mean of readings 2 + 3, and mean of readings 2 – 6)
- Diastolic blood pressure at each of trial visits 3 – 7 (mean of readings 2 + 3, and mean of readings 2 – 6)
- Mean arterial pressure at each of trial visits 3 – 7 (mean of readings 2 + 3, and mean of readings 2 – 6)
- Mean of systolic blood pressure readings 2+3, over visits 3 – 7 (i.e. 10 readings)

i.e. $SYSBP_{MeanV3-7}$ (derived variable) = $(Visit3\ SBP2 + Visit3\ SBP3 + Visit4\ SBP2 + Visit4\ SBP3 + Visit5\ SBP2 + Visit5\ SBP3 + Visit6\ SBP2 + Visit6\ SBP3 + Visit7\ SBP2 + Visit7\ SBP3) / 10$

- Mean of diastolic blood pressure readings 2+3 over visits 3 – 7 (i.e. 10 readings)
- Mean of mean arterial pressure readings 2+3 over visits 3 – 7 (i.e. 10 readings)
- Mean of systolic blood pressure readings 2-6 over visits 3 – 7 (i.e. 25 readings)

- Mean of diastolic blood pressure readings 2-6 over visits 3 – 7 (i.e. 25 readings)
- Mean of mean arterial pressure readings 2-6 over visits 3 – 7 (i.e. 25 readings)
- Trial blood pressure readings above or below safety thresholds (mean of readings 2+3; and mean of readings 2-6)
 - SBP $\geq$ 160 mmHg (on or off treatment)
 - DBP $\geq$ 110mmHg (on or off treatment)
 - SBP < 90 mmHg (on treatment)
- Trial blood pressure readings in target range (mean of readings 2+3; and mean of readings 2-6)
 - Target range on treatment: SBP < 140 mmHg > 100 mmHg AND DBP <90 mmHg > 60mmHg
 - Target range off treatment: SBP < 140 mmHg AND DBP < 90 mmHg
- Time to event: time elapsed from randomisation or from discharge from hospital after birth until a participant requires either an urgent visit to GP or hospital (analysed as a single variable) requiring medication increase due to BP > 150/100 mmHg, or medication decrease due to BP < 100 mmHg systolic
- Duration of postnatal blood pressure treatment from date of delivery to date of treatment cessation (days)

3.1.2.2 POSTNATAL READMISSION OUTCOME

We will calculate this for each group, and will report it in the following ways:

- Count data: total number of separate readmissions
- Binary data: total number of participants in each group who had at least one readmission

3.1.2.3 PATIENT EXPERIENCE

Data from the EQ-5D-5L quality of life questionnaires will be compared at three time points (screening, 6 weeks and 6 months after delivery) in each group.

- The EQ-VAS scores will be presented as a mean and standard deviation in each group at each time point.
- Data from each dimension (mobility; self-care; usual activities; pain/discomfort; anxiety/depression) from the EQ-5D-5L descriptive system will be presented as a mean and standard deviation in each group at each time point.

3.1.2.4 VASCULAR RISK MEASURES

These values will be presented as means with standard deviations for each group. These measures will be carried out at either baseline or visit 3 (i.e. any time from 1 – 14 days post-delivery), and 3 months (visit 6). The analysis will be adjusted for which day the measures are performed on.

Measures of arterial stiffness

Cardio-ankle vascular index: CAVI (ratio, left and right)

Aortic systolic pressure (mmHg)

Augmentation index, and augmentation index at HR75 (%)

Pulse wave velocity (m/s) + SD

Microvascular changes

Capillary densities will be calculated from the DVD recordings. 6 fields will be analysed in a standard way to count the capillaries visible within a circular field. For each participant the mean number of capillaries visible within the 6 fields will be calculated, and using the area of the circular field a capillary density per mm² will be calculated. For each participant the functional (resting) and anatomical (with a pressure cuff inflated to 60-80mmHg around the base of the finger) density will be calculated.

Fasting blood tests

Table 1: Fasting blood tests

LABORATORY ANALYSES	Units	Normal range (OUH)	Normal range (preg)
Haemoglobin	g/L	120 – 150	110 – 140
Platelets	x 10 ⁹ /L	150 – 400	150 – 400
Haematocrit	L/L	0.30 – 0.46	
Mean corpuscular volume	fl	83 – 105	80 – 100
Urea	mmol/L	2.5 – 6.7	2.0 – 4.2
Creatinine	micromol/L	49 – 90	24 – 68
Alanine transferase	IU/L	10 – 45	< 30
Alkaline phosphatase	IU/L	30 – 130	< 500
Uric acid	micromol/L	150 – 350	0.14 – 0.2/0.35
Total cholesterol (TChol)	mmol/L	≤ 5.0	
High density lipoprotein cholesterol (HDL Chol)	mmol/L	> 1.0	
Low density lipoprotein cholesterol (LDL Chol)	mmol/L	≤ 3.0	
TChol : HDL Chol ratio	N/A	< 4	
Triglycerides (TG)	mmol/L	0.55 – 1.90	
Insulin	pmol/L	< 174 (fasting)	
Glucose	mmol/L	< 7.8 (2 hours post oral glucose)	< 6.0 (fasting) < 8.0 (random)

3.1.2.5 SAFETY MEASURES

- Reporting of serious adverse events (end of trial period)

- Reporting of side effects (end of trial period)

3.1.3 EXPLORATORY ANALYSIS

- Assess percentage time spent in target BP range in both groups, and use the home monitoring data from the intervention arm to explore the validity of this measure and the relationship between the trial blood pressure readings taken at two time points (end of trial period)
- Difference between home and clinic BP recordings (end of trial period)
- Fasting blood tests (for novel markers of cardiovascular risk and pre-eclampsia)

3.2 TARGET POPULATION

Inclusion criteria:

- Participant is willing and able to give informed consent for participation in the study.
- Female, aged 18 years or above.
- Women with gestational hypertension (new-onset BP > 140/90mmHg) or pre-eclampsia (new onset BP > 140/90mmHg and significant proteinuria > 300mg/24hr), prior to their discharge from hospital post-delivery.
- Require antihypertensive medication during pregnancy, which needs to continue in the postpartum period.

Exclusion criteria:

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

- Hypertension prior to pregnancy.
- Poor English language skills.
- More than three antihypertensive agents at discharge from hospital postpartum.

3.3 SAMPLE SIZE

A formal sample size calculation is not required for this pilot study. We will aim to recruit 100 women (i.e. 50 women will be randomised to each arm).

The choice of sample size was based on recommendations given by Teare et al. (2014): They suggest a sample size of at least 70 is required to estimating the standard deviation of a normally distributed variable. They also discuss the potential for a larger sample size (60 per group) being advantageous when analysing the recruitment parameters for a trial but acknowledge the need to balance maximising the precision of a pilot study with minimising the size of an external pilot study to limit impact on time and resources (4).

The chosen sample size was based on the projected population size from which to recruit over a 9 month period. From the results of a 2-month coded database search, and subsequent medical record review at the main centre (Oxford University Hospitals NHS Trust), this estimated that 25 patients per month across the two sites (Oxford and Banbury) had gestational hypertension or pre-eclampsia which required antihypertensive medication after discharge from hospital postpartum. Given the relative sizes of the different centres we estimate that across the sites approximately 60 women per month might be eligible for the study. This equates to ~540 in 9 months, giving a required recruitment rate of approximately 20%.

3.4 RANDOMISATION AND BLINDING IN THE ANALYSIS STAGE

A secure web-based randomisation system has been provided by the Oxford Primary Care Clinical Trials Unit (Sortition V2.3): <https://ctu1.phc.ox.ac.uk/randomise/login>

The system will allow for the allocation of patients to the two treatment groups: standard care or self-management on a 1:1 basis and for this allocation to be stratified according to recruitment site.

Due to the nature of the intervention it will not be possible to blind patients, the recruiting clinician or data management staff within the clinical trials unit to the group allocation.

Blood pressure will be measured at the trial follow up visits using a validated, automated monitor.

4 ANALYSIS – GENERAL CONSIDERATIONS

4.1 DESCRIPTIVE STATISTICS

The analyses for this pilot study will be primarily descriptive and will not include any hypothesis testing or presentation of P-values for group comparisons.

Continuous variables will be reported as means with standard deviations (or medians with Interquartile ranges if skewed) by treatment group. Categorical variables will be reported as counts and percentages in each treatment group. Differences between groups will be calculated and described with 95% confidence intervals only and will not include significance tests with p-values.

4.2 CHARACTERISTICS OF PARTICIPANTS

The following demographic characteristics and baseline data will be used to assess the baseline comparability of randomised groups:

- Age
- Parity
- Ethnic origin
- Socioeconomic status (Index of Multiple Deprivation)
- BMI

- Diagnosis (gestational hypertension or pre-eclampsia)
- Gestation at diagnosis
- Duration of antenatal antihypertensive treatment (days)
- Gestation at delivery
- 'Amount' of antihypertensive treatment at baseline visit (WHO defined daily doses)
- Systolic and diastolic blood pressure at baseline visit (mean of readings 2 and 3)

Frequencies and percentages will be reported for categorical variables and for continuous variables, the mean and standard deviation will be reported if normally distributed, and the median and interquartile range if not. No formal statistical testing will be applied to test for any difference between randomised groups with respect to baseline characteristics.

4.3 DEFINITION OF POPULATION FOR ANALYSIS

For the primary outcome data (feasibility measures) the whole population will be analysed collectively.

The secondary analysis will be an intention to treat analysis. That is, after randomisation, participants will be analysed according to their allocated intervention group irrespective of what they actually receive.

For the purposes of the secondary analysis participants who miss a single visit, or who undergo one or more visits outside the scheduled time windows, or who withdraw from the study but consent to their data being used will be included in this analysis. Participants where there has been a protocol violation will also be included in the secondary analysis.

4.4 POOLING OF INVESTIGATIONAL SITES

The investigating sites are as follows:

- Oxford (John Radcliffe Hospital) – covering the region of Oxfordshire
- Banbury (Horton General Hospital) – covering North Oxfordshire and South Warwickshire
- Reading (Royal Berkshire Hospital) – covering Berkshire
- Northampton (Northampton General Hospital) – covering Northamptonshire
- Aylesbury (Stoke Mandeville Hospital) – covering Buckinghamshire

The randomisation will be stratified by site.

4.5 DATA MONITORING COMMITTEE AND INTERIM ANALYSES

An independent data monitoring and ethics committee (DMEC) has been set up: The study is being undertaken in a population who have recently given birth, and therefore have the potential to be

more vulnerable. The study involves a novel complex intervention, which has not been evaluated in this context. The study is being run across several centres. For these reasons during the study design we felt it was prudent to appoint an independent DMEC.

The DMEC is comprised of two independent Obstetricians with research interests in this area, and an independent Statistician. This DMEC will meet as a minimum on an annual basis.

This committee will be unblinded.

They will receive an interim report from the trial team 6 months after commencement of the trial. During the preparation of this report the trial team will be blinded to participant allocation. The purpose of this analysis is to ensure the safety of trial participants, and to identify issues with recruitment or allocation imbalance. This will contain the following information:

- Recruitment to date (total and stratified by centre)
- Recruitment based on eligibility
- Allocation balance
- Comparability of baseline characteristics:
 - Age
 - Ethnicity
 - Systolic blood pressure at visit 2 (baseline) – mean of readings 2 and 3
- Compliance rate (number of study visits attended / expected number of study visits within given time frame)
- Secondary outcome measure: number of trial blood pressure readings ≥ 160 systolic or ≥ 110 diastolic at follow up visits 3, 4 and 5
- Adverse event rate disaggregated by events considered as 'serious' and 'not serious' and whether 'possibly related' or 'probably unrelated' to the trial

The information to be contained in the DMEC report will be described in more detail in the DMEC report template.

There are no formal stopping rules. It has been agreed that the DMEC would only recommend stopping based on safety concerns (SAE reports / significant differences in high BP at trial visits).

As this is a pilot study no additional interim analysis is planned.

5 PRIMARY ANALYSIS

5.1 PRIMARY OUTCOME

The primary objective is to assess feasibility measures. For this analysis, the following parameters will be expressed as counts and percentages. There will be no formal hypothesis testing using statistical tests performed between randomised groups. In the primary analysis these measures will be performed with 'end of study' as the time point unless otherwise specified. In the case of the retention rate we also plan to calculate this at 6 weeks (visit 5) as this is a possible endpoint for a future larger study.

- Recruitment rate

$$= (\text{number randomised (n)} / \text{number of participants approached}) \times 100\%$$

$$= (\text{number randomised (n)} / \text{number of eligible participants approached}) \times 100\%$$

- Recruitment rate per site per month

$$= (\text{number randomised (n)} / \text{cumulative recruitment period (months)})$$

Cumulative recruitment period is equal to the sum of all the recruitment periods (months) across all sites

- Consent rate

$$= (\text{number consented} / \text{number of participants approached}) \times 100\%$$

- Conversion rate

$$= (\text{number randomised} / \text{number of participants consented}) \times 100\%$$

- Retention rate

$$= (\text{number completing follow-up to 6 months} / \text{number randomised (n)}) \times 100\%$$

$$= (\text{number completing follow-up to 6 weeks} / \text{number randomised (n)}) \times 100\%$$

- Compliance rate

$$= (\text{number of study follow-up visits (3 – 7) attended within pre-defined time window} / \text{total number of intended study follow-up visits (3 – 7)}) \times 100\%$$

$$= (\text{number of study follow-up visits (3 – 7) attended} / \text{total number of intended study follow-up visits (3 – 7)}) \times 100\%$$

These will be calculated for the whole randomised population, and for the randomised population minus women withdrawn from the study.

Criteria for success of this pilot study:

- Recruitment rate:
 - Minimum of 3 participants recruited per week across all sites
 - No centre to contribute < 5% of study participants
- Attrition rate of < 10%
- Compliance rate > 90%

5.2 HANDLING MISSING DATA

As part of the primary objective of assessing feasibility, the rate of missing data is highly relevant and is an important outcome in the final report. The rate of missing values will be summarised. Data on attrition rates, compliance (as detailed above) and completion of outcome measures will also be summarised.

We will not impute any missing data for any of the analyses specified in this analysis plan for the same reason given above.

5.3 HANDLING OUTLIERS

A possible outlier is defined as a data-point three standard deviations from the mean of its distribution in the variable at the time-point. For outliers that have not been already queried in data cleaning, they will be queried for double-checking at this stage.

6 SECONDARY ANALYSIS

6.1 SECONDARY OUTCOMES

The secondary outcomes comprise a range of measures of efficacy, performed over the 6 month follow-up period. Secondary outcomes have been grouped by variable type. Analysis will be conducted on all patients randomised.

6.1.1 BINARY OUTCOMES

Binary secondary outcomes (e.g. number of participants with at least one postnatal readmission) will be analysed by presenting the frequency and proportion in each randomised group. A log binomial model will be fitted to the data with randomised group and recruitment site as covariates. Adjusted relative risks and 95% confidence intervals will be presented. The log-binomial regression model may be unstable at low event rates. If the number of events is less than 20, the results obtained from the log-binomial regression model will be interpreted with caution. In addition, the difference in the proportions of patients having an event between the treatment arms and 95% CI for this difference will be computed using the Newcombe-Wilson Method².

6.1.2 REPEATED MEASURES OUTCOMES

Systolic blood pressure, diastolic blood pressure, arterial pressure, EQ-VAS scores, EQ-5D-5L descriptive system for each dimension, EQ-5D-5L descriptive system with the Crosswalk Index Value) will be analysed using a mixed effects regression model with repeated measures. The mean of BP

readings 2 and 3 will be used as one outcome, and the mean of readings 2-6 as a separate outcome. The model will include the outcome with randomised group, time and an interaction between time and randomised group as fixed effects. The model will adjust for recruitment site and blood pressure at baseline, also fitted as a fixed effect with an unstructured covariance pattern. The difference in the adjusted means between the treatment groups with 95% confidence intervals at each time point will be presented.

There will be an assessment of the use of time as a random slope in the model. The model assumptions will be explored by assessing the departure from normality using residual and diagnostic plots. If the assumptions seem to be violated, either a transformation to the data or non-parametric methods will be used.

6.1.3 CONTINUOUS OUTCOMES

One value per participant (average systolic blood pressure over visits, average diastolic blood pressure over visits, duration of postnatal antihypertensive treatment, arterial pressure, arterial stiffness, aortic blood pressure and augmentation index, functional and anatomical capillary density and circulating biomarkers (routine pre-eclampsia blood tests and cardiovascular risk markers including lipid profile and glucose) will be analysed by presenting the mean and standard deviation (or median and interquartile range if the data is skewed) by treatment group. A linear regression model for the mean combined pressures at visits 3-7 will be fitted with treatment group as the independent variable and adjusting for recruitment centre and mean blood pressure at baseline. The assumptions of the model will be explored and if the assumptions are violated, either a transformation to the data or non-parametric methods will be used. This model will not be applied to the vascular risk measures as the population for this analysis is too small.

6.1.4 TIME TO EVENT OUTCOMES

Time to urgent GP or hospital visit (analysed as a single variable) from both randomisation and date of discharge will be analysed by presenting the event rate in each treatment group as well as the median, interquartile range and range for the duration to event in each treatment group. A Kaplan-Meier plot of the survival curves for each treatment group will be presented. A Cox proportional hazards model will be fitted to the data with time to GP or hospital admission as the outcome, including randomised group and recruitment site in the model. The assumptions of the Cox model will be explored and if any assumptions are violated alternative methods will be used to analyse the data. The Cox regression model may be unstable when the event rate is low. If the number of events (i.e. urgent GP or hospital visit) is less than 20 the results obtained from the Cox regression model will be interpreted with caution.

6.1.5 COUNT OUTCOMES

Number of separate readmissions will be analysed by presenting the event rate in each treatment group. A negative binomial model will be fitted to the data to compare randomised groups. The dependent variable is the number of readmissions while the explanatory variables will include randomised group and recruitment site. The incidence rate ratio and 95% confidence interval will be reported. If there are less than 20 participants with at least one postnatal admission, the negative binomial regression model may be unstable. Results obtained from this model will be interpreted with caution.

6.1.6 GROUPED BINARY OUTCOMES

Blood pressure readings in target range: A logistic regression model for grouped data (number of times target BP in range/number of time points BP measured) will be fitted with randomised group and recruitment centre fitted as covariates. Adjusted odds ratio and 95% confidence interval will be presented.

7 SUBGROUP ANALYSES

There will be no subgroup analyses for this pilot study.

8 ADDITIONAL ANALYSES

8.1 PRIMARY OUTCOME

The feasibility parameters will also be calculated at different time points in the study, in view of that fact that during a large-scale multicentre trial it will likely be impractical to follow all women up for 6 months: Instead we will determine the duration of follow up until blood pressure levels return to their normal range following treatment cessation.

We will therefore calculate the feasibility parameters (as described above in section 5.1) at both the 6-week and 3-month follow-up time points.

8.2 COMPLETION OF INTERVENTION

For the intervention group we will calculate the rate of 'completion of intervention':

- Completion of intervention = number of women in intervention group who either complete home monitoring to the end of treatment + further 5 readings OR women who complete home monitoring to follow-up at 6 months (whichever is sooner) / total number of women in intervention group

8.3 SECONDARY OUTCOMES

We will analyse mean blood pressure parameters at different time points, as by the end of the study (6 months postpartum) we expect approximately 95% to have normalised their blood pressure and no longer require treatment.

A linear regression model for the mean systolic pressure (readings 2-3 and readings 2-6), diastolic pressure (as for systolic) and mean arterial pressure (as for systolic) at visits 3-5 will be fitted with treatment group as the independent variable and adjusting for recruitment centre and mean pressure at baseline. A further regression will be done for the same blood pressure parameters, with the same adjustments, at visits 3-6.

8.4 EXPLORATORY ANALYSES

We will explore the validity of a 'time in range' measure as previously described in the analysis of the management of oral anticoagulant therapy by Rosendaal et al in 1993.³

In the intervention group we will explore the difference between the home and trial visit (clinic) blood pressure measurements.

We will have two datasets for the home blood pressure measurements for each participant in the intervention group: one will be generated from the readings the participant submits via the SMS service or smartphone app; the other will be from the blood pressure monitor's memory, in which 200 readings can be stored, and which can be downloaded to a computer. Presenting the percentage of measurements reported both incorrectly and incorrectly with clinical significance will allow a comparison between the accuracy with which participants transcribe and report their blood pressure readings while distinguishing between a discrepancy and a clinically significant discrepancy.

Table 2: Novel serum markers for pre-eclampsia and cardiovascular risk

RESEARCH ANALYSES	Units	Range
eSelectin	pg/ml	93.8 – 6000.0
Myeloperoxidase (MPO)	ng/ml	0.156 – 10.000
Soluble intercellular adhesion molecule-1 (sICAM1)	ng/ml	
Soluble vascular intercellular adhesion molecule-1 (sVCAM1)	ng/ml	6.25 – 200.00
Tissue plasminogen activator inhibitor-1 (tPAI1)	pg/ml	78.1 – 5000.0
Transforming growth factor beta (TGF-β)	pg/ml	31.2 – 2000.0
Soluble endoglin (sENG)	ng/ml	0.156 – 10.000
Vascular endothelial growth factor (VEGF)	pg/ml	31.2 – 2000.0
Soluble fms-like tyrosine kinase-1 (sFLT1)	pg/ml	31.2 – 2000.0
Matrix metalloproteinase-2 (MMP2)	ng/ml	0.312 – 20.000
Matrix metalloproteinase-9 (MMP9)	ng/ml	0.5 – 32.0
Placental growth factor (PLGF)	pg/ml	15.6 – 1000.0
Adiponectin	ng/ml	3.9 – 250.0
Leptin	pg/ml	15.6 – 1000.0
Visfatin	ng/ml	0.50 - 32
Resistin	ng/ml	0.16 – 10.00
High sensitivity C-reactive protein (HsCRP)	ng/ml	0.78 – 50.00
Galectin-1	ng/ml	0.313 – 20.000
Galectin-3		0.313 – 10.000
Galectin-9		0.156 – 10.000
Atrial natriuretic peptide (ANP)	pg/ml	15.60 - 1000
Microparticles		
<i>Homeostatic model assessment of insulin resistance (HOMA-IR)</i>		
<i>Homeostatic model assessment beta-cell function (HOMA-β)</i>		
Interleukin-10 (IL10)	pg/ml	7.8 – 500.0
Interleukin-6 (IL6)	pg/ml	3.12 – 300.00
Interleukin-8 (IL8)	pg/ml	31.2 – 2000.0
Monocyte chemoattractant protein-1 (MCP-1)	pg/ml	31.2 – 2000.0
Tumour necrosis factor alpha (TNFα)	pg/ml	15.6 – 1000.0

We will look at range of novel serum markers (Table 2) for pre-eclampsia and cardiovascular risk (including fasting insulin, glucose, HOMA, CRP and other novel proposed risk factors such as adhesion molecules and adipokines). These will be measured at either the baseline visit or visit 3 (i.e.

from day 1 – 14 post-delivery) and at visit 6 (3 months). The mean and standard deviation (or median and interquartile range, if skewed) of the markers will be presented by treatment group. The markers will be analysed in a similar way to the continuous outcomes in section 6.1 by fitting a linear regression model for the mean combined markers across the visits with treatment group as the independent variable while adjusting for centre and the mean of the marker at baseline.

9 SAFETY ANALYSIS

9.1 ADVERSE EVENTS

Adverse event reporting will take place in all participants in both groups from baseline to 6-month follow-up. Participants will be able to report adverse events by telephone, email, SMS or via the smartphone app. They will also be able to report adverse events in person at the trial follow up visits. Additionally the SMS service and smartphone app used by participants in the intervention group will automatically record adverse events if a blood pressure of ≥ 160 mmHg or ≥ 110 mmHg, or < 90 mmHg systolic and < 50 mmHg diastolic is submitted by a participant.

An adverse event will be classified as serious if it:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;
- Consists of a congenital anomaly or birth defect.

Serious adverse events will be recorded and reported in both groups. This will be expressed as counts and percentages (both total number of SAEs, and the total number of participants affected by SAEs), and will be further classified according to expectedness and relatedness.

A SAE occurring to a participant will be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event is 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Related and unexpected SAEs will also be reported to the sponsor. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event.

10 QUALITY ASSURANCE

The statistical analysis will be carried out by the Chief Investigator, but will be validated by an independent statistician at the Primary Care Clinical Trials Unit.

11 CHANGES TO THE PROTOCOL OR PREVIOUS VERSIONS OF SAP

Amendment no.	New SAP version no.	Date issued	Author(s) of changes	Details of changes made

12 REFERENCES

1. Podymow T, August P. Postpartum course of gestational hypertension and preeclampsia. *Hypertens Pregnancy*. 2010;29(3):294-300.
2. Lazdam M, de la Horra A, Diesch J, Kenworthy Y, Davis E, Lewandowski AJ, et al. Unique blood pressure characteristics in mother and offspring after early onset preeclampsia. *Hypertension*. 2012;60(5):1338-45.
3. Chung Y, de Greeff A, Shennan A. Validation and compliance of a home monitoring device in pregnancy: microlife WatchBP home. *Hypertens Pregnancy*. 2009;28(3):348-59.
4. Teare MD, Dimairo M, Shephard N, Hayman A, Whitehead A, Walters SJ. Sample size requirements to estimate key design parameters from external pilot randomised controlled trials: a simulation study. *Trials*. 2014;15:264.

13 APPENDICES

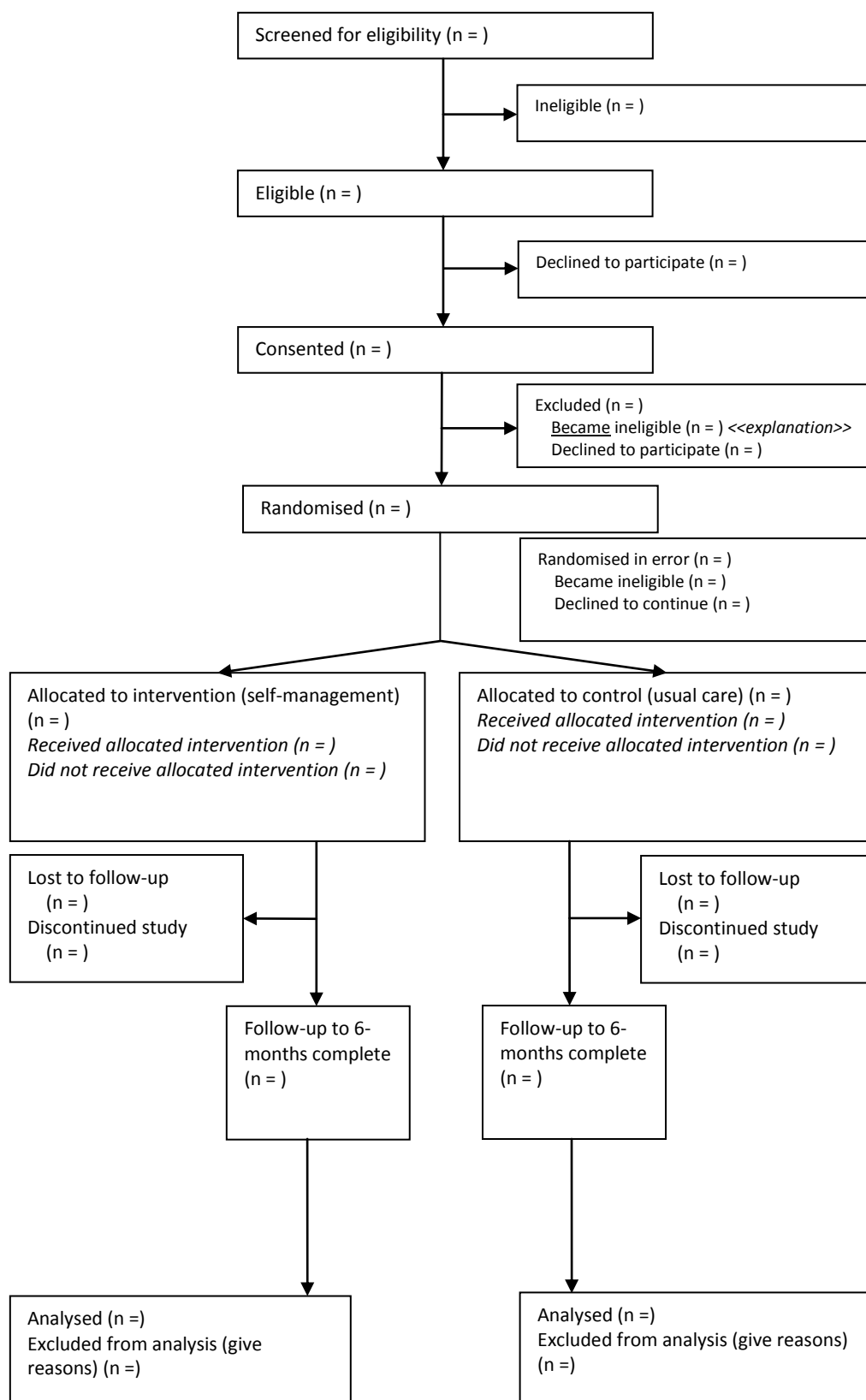
13.1 APPENDIX I. SCHEDULE OF PROCEDURES

Procedures	Visits (all timings in relation to date of delivery)						
	1: Screening	2: D3 ±2d	3: D10 ±2d	4: 4w ±5d	5: 6w ±1w	6: 12w ±1w	7: 26w ±2w
Informed consent	X						
Verbal confirmation of consent		X	X	X	X	X	
Demographics	X	X					
Medical history	X	X					
Eligibility assessment	X						
Eligibility confirmation		X	X	X	X	X	X
Randomisation		X					
Blood pressure check		X	X	X	X	X	X
Document medications	X	X	X	X	X	X	X
Side effect check		X	X	X	X	X	X
Adverse event assessment			X	X	X	X	X
Weight	Record booking weight	X				X	X
EQ-5D-5L	X				X		X
Offer specialist hypertension assessment if on-going treatment					X		
Structured patient experience interview (optional)	X			X			X
Vascular risk measurements (optional)		X				X	

13.2 APPENDIX II. OUTCOME ASSESSMENT SCHEDULE

		Visits (all timings in relation to date of delivery)						
		1: Screening	2: D3 ±2d	3: D10 ±2d	4: 4w ±5d	5: 6w ±1w	6: 12w ±1w	7: 26w ±2w
Primary outcome								
Recruitment rate	All feasibility outcome measures will be calculated for the whole study population at the end of the trial period (defined as when the last participant completes their final follow up visit).							
Retention rate								
Attrition rate								
Compliance rate								
Secondary outcomes								
Systolic BP			X	X	X	X	X	
Diastolic BP			X	X	X	X	X	
Mean arterial pressure			X	X	X	X	X	
Urgent visits to GP for poorly controlled BP	From baseline to visit 7 all urgent visits to a GP or hospital requiring medication adjustment due to SBP > 150 mmHg or DBP > 110 mmHg will be documented							
Postnatal readmission rate	From baseline to visit 7 all postnatal readmissions to hospital will be documented							
EQ-5D-5L	X				X		X	
Structured interviews	X			X			X	
Laboratory values		X				X		
Arterial stiffness measures		X				X		
Microvascular changes		X				X		
Exploratory analysis								
% time spent in target BP range			X	X	X	X	X	
HBPM vs clinic BPM difference (intervention group only)			X	X	X	X	X	
Novel serum markers of vascular risk		X (or visit 3)				X		
Safety analysis								
Serious adverse events	From baseline to visit 7 all serious adverse events will be recorded							
Key covariates								
Demographics (age, ethnicity)	X	X						
Baseline systolic BP (mean of readings 2+3)		X						

13.3 APPENDIX III. CONSORT FLOW DIAGRAM OF TRIAL PARTICIPANTS



Appendix 15: CONSORT 2010 checklist

Information to include when reporting a randomised trial (adapted to incorporate recommendations from CONSORT 2010 statement: extension to randomised pilot and feasibility trials (1))*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot of feasibility randomised trial in the title	#1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	#2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	#3
	2b	Specific objectives or research questions for pilot trial	#3
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	#4
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	#4
	4b	Settings and locations where the data were collected	#4
	4c	How participants were identified and consented	#4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	#4-5
Outcomes	6a	Completely defined pre-specified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	#5
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	N/A
	6c	If applicable prespecified criteria used to judge whether, or how, to proceed with future definitive trial	#5
Sample size	7a	Rationale for numbers in the pilot trial	#6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	#6
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	#4
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	#4

* We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	#4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	#4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	N/A
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Methods used to address each pilot trial objective whether qualitative or quantitative	#6
	12b	N/A (methods for additional analyses, such as subgroup analyses and adjusted analyses)	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	#6-7, 16 (diagram)
	13b	For each group, losses and exclusions after randomisation, together with reasons	#6-7, 16 (diagram)
Recruitment	14a	Dates defining the periods of recruitment and follow-up	#6
	14b	Why the pilot trial ended or was stopped	#6-7
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	#17
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	#7, 18-19, 21
Outcomes and estimation	17a	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	#7-8, 18-21, Appendices 3-6
	17b	N/A (for binary outcomes, presentation of both absolute and relative effect sizes is recommended)	
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	#8
Harms	19a	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	#8, Appendix 8
	19b	If relevant, other important unintended consequences	
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	#10
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	#9-11
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	#9-12
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	#6
Protocol	24	Where the pilot trial protocol can be accessed, if available	#4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	#1, 2 & 6
Ethics	26	Ethical approval or approval by research review committee, confirmed by reference number	#4

1. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *Bmj*. 2016;355:i5239.



Self-mANagement of Postnatal anti-Hypertensive Treatment SNAP-HT Trial Development Pilot Study

APPENDIX 16: SNAP-HT interview template

Patient experience semi-structured interview: template

Researcher initials/ Date of interview	e.g. AC / 27-Aug-2014	Participant's Study ID	SNAP- -
Record group	Intervention / Control	Visit number (1/4/7)	

We are going to ask you some questions that relate to the raised blood pressure you have developed during your pregnancy.

Part 1	For all participants (including those in the control group) at visits 1, 4 and 7

On a scale of 1 to 5 (1 being the least and 5 being the most) please indicate how participant rated the following questions:

1. How much in control do you feel of managing your condition?	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr><td>1. Do not feel in control</td></tr> <tr><td>2.</td></tr> <tr><td>3.</td></tr> <tr><td>4.</td></tr> <tr><td>5. Very much feel in control</td></tr> </table>	1. Do not feel in control	2.	3.	4.	5. Very much feel in control	Explain why:
1. Do not feel in control							
2.							
3.							
4.							
5. Very much feel in control							
2. How confident are you about taking an <i>active</i> part in the conversation when discussing your condition with health care professionals?	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr><td>1. Not confident at all</td></tr> <tr><td>2.</td></tr> <tr><td>3.</td></tr> <tr><td>4.</td></tr> <tr><td>5. Very confident</td></tr> </table>	1. Not confident at all	2.	3.	4.	5. Very confident	Explain why:
1. Not confident at all							
2.							
3.							
4.							
5. Very confident							
3. How much do you feel you are sharing responsibility of your treatment with a health professional?	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr><td>1. Do not feel that I am sharing responsibility</td></tr> <tr><td>2.</td></tr> <tr><td>3.</td></tr> <tr><td>4.</td></tr> <tr><td>5. Very much feel that I am sharing responsibility</td></tr> </table>	1. Do not feel that I am sharing responsibility	2.	3.	4.	5. Very much feel that I am sharing responsibility	Explain why:
1. Do not feel that I am sharing responsibility							
2.							
3.							
4.							
5. Very much feel that I am sharing responsibility							
<i>Continued overleaf</i>							

4. How knowledgeable do you feel about your condition?	1. Do not feel knowledgeable	Explain why:
	2.	
	3.	
	4.	
	5. Feel very knowledgeable	
5. To what extent has your condition impacted on your relationships with family and friends?	1. Not able to maintain good relationships	Explain why:
	2.	
	3.	
	4.	
	5. Very much able to maintain good relationships	

Continue to part two at visit 4 and 7 if participant is part of intervention group

Part 2	For the intervention group only at visits 4 and 7	
6. The materials that you are using as part of the self-management: how well do you think they fit with managing your condition?	1. Do not fit with managing my condition	Explain why:
	2.	
	3.	
	4.	
	5. Fit very well with managing my condition	
7. How easy or difficult are you finding the self-management materials to operate?	1. Very difficult to operate	Explain why:
	2.	
	3.	
	4.	
	5. Very easy to operate	
<i>Continued overleaf</i>		

8. Have you seen a change in your lifestyle for better or for worse since starting self-management?	<table border="1"> <tr><td>1. Change in lifestyle for worse</td></tr> <tr><td>2.</td></tr> <tr><td>3.</td></tr> <tr><td>4.</td></tr> <tr><td>5. Change in lifestyle for better</td></tr> </table>	1. Change in lifestyle for worse	2.	3.	4.	5. Change in lifestyle for better	Explain why:
1. Change in lifestyle for worse							
2.							
3.							
4.							
5. Change in lifestyle for better							
9. How likely are you to recommend the self-management of gestational hypertension / pre-eclampsia to friends, family and other people?	<table border="1"> <tr><td>1. Not likely</td></tr> <tr><td>2.</td></tr> <tr><td>3.</td></tr> <tr><td>4.</td></tr> <tr><td>5. Very likely</td></tr> </table>	1. Not likely	2.	3.	4.	5. Very likely	Explain why:
1. Not likely							
2.							
3.							
4.							
5. Very likely							
10. How likely are you to use self-management approaches to manage medical conditions in the future?	<table border="1"> <tr><td>1. Not likely</td></tr> <tr><td>2.</td></tr> <tr><td>3.</td></tr> <tr><td>4.</td></tr> <tr><td>5. Very likely</td></tr> </table>	1. Not likely	2.	3.	4.	5. Very likely	Explain why:
1. Not likely							
2.							
3.							
4.							
5. Very likely							

Additional notes / researcher reflections: