Effect of self-monitoring of blood pressure on diagnosis of hypertension during higher-risk pregnancy: the BUMP 1 randomized trial

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Key Points (88 words)

Question: Does self-monitoring of blood pressure by pregnant individuals at higher risk of pre-eclampsia lead to earlier detection of pregnancy hypertension compared to usual antenatal care?

Findings: In this randomized clinical trial that included 2441 pregnant individuals at increased risk for pre-eclampsia, use of self-monitoring of BP with telemonitoring compared with usual care resulted in a mean time to clinic-based detection of hypertension of 104 vs 106 days, a difference that was not statistically significant.

Meaning: Among pregnant individuals at higher risk of pre-eclampsia, blood pressure self-monitoring with telemonitoring did not lead to earlier clinic-based detection of hypertension.

Abstract

Importance: Inadequate management of elevated BP is a significant contributing factor to maternal deaths. Self-monitoring of blood pressure (BP) in the general population has been shown to improve the diagnosis and management of hypertension, however little is known about its use in pregnancy.

Objective: To determine whether self-monitoring of BP in higher risk pregnancies leads to earlier detection of pregnancy hypertension.

Design, setting and participants: Unmasked, randomised clinical trial that recruited between November 2018 and October 2019. 2441 pregnant individuals at higher risk of pre-eclampsia were recruited at 20 weeks' gestation from 15 hospital maternity units in England with final follow-up in April 2020.

Interventions: Participating individuals were randomised to either BP self-monitoring with telemonitoring (n=1223) plus usual care or usual antenatal care alone (n=1218) without access to telemonitored BP.

Main Outcomes: The primary outcome was time to first recorded hypertension measured by a healthcare professional.

Results: Among 2441 participants who were randomized (mean age, 33; median gestation 20 weeks), 2346 (96%) completed the trial. The time from randomisation to clinic recording of hypertension was not significantly different between individuals in the self-monitoring group (mean 104 days) vs the usual care group (mean 106 days) (mean difference -1.6 days (95% confidence intervals -8.1, 4.9, p = 0.6). Eighteen serious adverse events were reported during the trial with none judged as related to the intervention: 12 (1%) in the self-monitoring group and 6 (0.5%) in those receiving usual care.

Conclusions and relevance: Among pregnant individuals at higher risk of pre-eclampsia, blood pressure self-monitoring with telemonitoring compared with usual care did not lead to significantly earlier clinic-based detection of hypertension.

Trial Registration: ClinicalTrials.gov NCT03334149 https://clinicaltrials.gov/ct2/show/NCT03334149

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INTRODUCTION

Raised blood pressure (BP) has been estimated to affect approximately 10% of pregnancies worldwide and 18 million pregnancies worldwide in 2019.[1,2] In the UK, inadequate management of elevated BP has previously been reported as a significant contributing factor to maternal deaths. Although maternal deaths related to high BP have reduced in the UK in recent years, pre-eclampsia remains important due to its influence on maternal and perinatal outcomes.[3,4] Individuals who are at higher risk of pre-eclampsia, due to risk factors such as age, high body mass index, or existing medical conditions may require more frequent monitoring.[5] BP can increase rapidly in pregnancy and hypertension may go undetected in between antenatal visits.[6]

Self-monitoring of blood pressure (SMBP), which involves an individual measuring their own BP outside of the clinical setting, is now commonplace and effective at detecting and lowering BP in adults with hypertension outside of pregnancy. [7-9] Self-monitoring in pregnancy has been limited to small and mostly non-randomized feasibility studies, often without validated BP monitors.[10,11] Low quality and heterogeneity limit the conclusions that can be drawn from such studies but initial results suggest reduced morbidity and resource use, acceptability for individuals and their clinicians, and feasibility. [10-13]

The Blood Pressure Monitoring in Higher Risk Pregnancy (BUMP1) trial aimed to establish whether SMBP with telemonitoring in addition to usual care could lead to earlier detection of raised clinic BP compared to usual care during higher risk pregnancies.

METHODS

Study design

The trial was an unmasked randomised clinical trial of SMBP in pregnancy for the detection of raised BP. The methods of the trial and its development have been published previously and are summarised below.[14,15] The protocol and statistical analysis plan are available in Supplement 1 and Supplement 2, respectively. The West Midlands - South Birmingham NHS Research Ethics Committee: ref 17/WM/0241 provided ethical approval. All participants gave written informed consent.

Study Population

Pregnant individuals at higher risk of pre-eclampsia were recruited by research midwives through antenatal clinics in 15 secondary care maternity units between 16 and 24 weeks gestation between November 2018 and September 2019. 'Higher risk' was defined by the relevant UK guidance at the time and included one or more of the following risk factors for pregnancy hypertension[5]: age ≥40 years nulliparity pregnancy interval >10 years, family history pre-eclampsia, previous history pre-eclampsia or gestational hypertension, body mass index ≥30 kg/m^2, chronic kidney disease (any CKD stage), twin pregnancy, pre-pregnancy diabetes, autoimmune disease (for example systemic lupus erythematosus or antiphospholipid syndrome). Individuals with a pre-existing diagnosis of hypertension were excluded.

Randomisation and masking

Eligible individuals were randomised (1:1 ratio) to either usual care or usual care plus SMBP with telemonitoring. The online randomisation sequence was generated by an independent statistician using permutated varying block sizes of 4 or 6 and stratified by recruitment site and parity (0 vs ≥1).

Both participants and health care professionals were unmasked due to the nature of the intervention.

Procedures

Self-monitoring

Participants randomised to SMBP continued with usual antenatal care and in addition were provided with a validated automated monitor (Microlife WatchBP Home).[16] They were given training and written instructions for BP self-monitoring by the recruiting research midwife, then enrolled on a mobile phone-based telemonitoring system with an optional paper diary.

Participants were asked to monitor their BP three times a week, taking two readings, submitting the second to the study App manually. Raised readings triggered a request by the app for a third reading, which if raised led to a request by the app for participants to contact their local maternity unit [eFigure 3]. Initial contact was typically by telephone and subsequent arrangements for review were at the discretion of the unit. BP thresholds were equivalent to clinic, based on pilot work and a systematic review. [13,17]

Each site received training on the trial and intervention from the study team. Clinicians had access to a web-based dashboard and each site was sent a summary of their participants' results each week. The app was designed to include a historic blood pressure data enabling participants to share their results with clinicians via their mobile phone display.

Usual prenatal care consisted of pregnant individuals attending antenatal clinic as required (at least seven times during an uncomplicated pregnancy)[18] including having their BP measured by their

antenatal care team. They did not have access to the telemonitoring system and such systems were not commonplace in the UK at the time of the study.

Protocol Amendments

The overall protocol was amended significantly on six occasions during the trial. Two amendments affected the trial: adding the external pilot and then to continue recruitment until the accompanying trial[14] (same intervention in individuals with pregnancy hypertension) had finished recruitment which had the effect of modestly increasing the sample size (from 2262 to 2441).

Outcomes

The primary outcome was difference in the time from randomisation to first recording of 'clinic hypertension' between the randomised groups. Clinic hypertension was defined as sustained BP ≥140/90mmHg [i.e. either raised systolic (SBP) or diastolic (DBP) blood pressure or both] recorded by a healthcare professional in the clinical record in any setting up to the day before delivery. 'Sustained' was defined as at least two raised BP readings within one week (168 hours) with no minimum time between readings, with the second reading date taken as date of diagnosis.[5] Clinic hypertension was additionally defined when either a recorded diagnosis of pre-eclampsia or gestational hypertension or prescription of antihypertensive medication where those came before recorded clinic hypertension. BP and other clinical data were extracted from the clinical record at the end of each woman's participation in the trial. Prespecified subgroups were: eligible for aspirin prophylaxis; gestational age at recruitment; parity; measuring BP prior to randomisation; deprivation score; ethnicity; educational qualifications.

Secondary outcomes were both maternal (severe hypertension (systolic BP ≥160 mmHg and/or diastolic BP ≥110 mmHg), serious maternal complications, onset of labour) and perinatal (stillbirth and early neonatal death, gestation at delivery, mode of delivery, birth weight (including centiles),

small for gestational age (<10th and <3rd centiles), neonatal admissions). Patient reported outcomes (illness perception (0 to 10, minimally clinically important difference [MCID] not available),[19] anxiety ((STAI6, scaled to 100 lowest 0 to highest 100, MCID 10),[20] maternal health-related quality of life (EuroQol EQ-5D-5L, -0.594 (worst) to +1 (best), MCID 0.037))[21] were captured by questionnaires at baseline, 30 weeks gestation and 12 weeks postnatally [See eTable 1 for full list]. In accordance with UK recommendations, self-reported ethnicity was recorded using standard descriptions derived from those used by UK Office for National Statistics.[22]

Post hoc analyses assessed fidelity of participants in the intervention group to the self-monitoring regime as captured by the App and compared raised BP on self-monitoring to the reference standard of raised BP on clinic measurements.

Sample size

An external pilot phase including 40 participants tested all trial procedures prior to the main trial commencing. A sample size of 2262 (1131 per group) assuming a standard deviation (SD) of 40 days was estimated to allow detection of an effect size of 12 days difference in time to detection of clinic hypertension in pregnancy between self-monitoring and control groups, with 90% power, 5% level of significance (2-sided) and assuming a 15% attrition rate. The sample size was determined via simulation, using a bootstrapping method with replacement with parameters derived from pilot work.[13] Of the planned 2262 participants, 362 (16%) were expected to develop hypertension. A statistical analysis plan was agreed prior to data lock (Supplement 2).

Statistical analysis

The primary analysis included all participants for whom data were available, according to the group participants were randomly allocated to regardless of any subsequent deviation from protocol. The primary outcome was analysed using a two-part "hurdle" model[23]: first the model determined

whether the participants had a diagnosis of clinic hypertension using a probit model, assuming an underlying latent distribution for the probability of having clinic hypertension. The second part determined the time between randomisation and clinic hypertension conditional on having cleared the hurdle. The pre-specified model adjusted for group, parity (0 or ≥1) as fixed effects, and site as random effect. However, because the model would not converge, site was subsequently fitted as a fixed effect. Sensitivity analyses included adjusting for baseline covariates that predicted missingness, multiple imputation (100 imputations) of missing values, and including only raised BP based on BP values (i.e. not clinical diagnoses or antihypertensive prescription). Prespecified subgroups were investigated through fitting a subgroup by randomised group interaction term in the model. Treatment effects of each subgroup and a test of interaction were obtained from the model.

Continuous secondary outcomes, such as birthweight and length of stay, were analysed by means of regression method, adjusting for stratification factors. Binary secondary outcomes were analysed by means of a log binomial model. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory.

Post hoc analyses were undertaken assessing intervention fidelity comparing app use to the protocol of thrice weekly self-monitoring until BP rose to ≥135/85mmHg when participants were asked to monitor daily until delivery or hypertension diagnosis. Recorded hypertension in clinic or by SMBP was cross tabulated and the time between first raised SMBP and subsequent diagnosis of hypertension assessed using similar methods to the primary outcome analysis (second part).

All analyses were performed using STATA SE version 16.1 (StataCorp) using a 5% threshold for significance (2-sided).

RESULTS

Of 2458 potentially eligible pregnant individuals, 2441 were randomised to either BP self-monitoring (n=1223, 50.1%) or usual care (n=1218, 49.9%) (in line with the randomisation algorithm) [Figure 1]. Four participants subsequently found to be ineligible after randomisation, were immediately withdrawn from the trial and excluded from the analysis.

Primary outcome data were available from 2346/2437 participants (96%, 1171 self-monitoring, 1175 usual care) [Figure 1]. Baseline characteristics were well matched between groups with similar demographics and risk factors for hypertension and pre-eclampsia [Table1]. Mean age was 33 years old, mean gestation was 20 weeks, 950/2346 (39%) were of parity ≥1, 1399/2346 (59%) had been educated to at least degree level, 1801 (77%) were White British, 253 (11%) Asian or Asian British and 187 (8%) Black or Black British. Mean BP recorded before randomisation was 114/69mmHg and 1146 (49%) had one major or two moderate risk factors for pre-eclampsia.[5] Prior to randomisation, 639/2414 (27%) participants reported previously measuring their own BP (305 (25%) intervention and 334 (28%) usual care).

Primary Outcome

Clinic hypertension was subsequently recorded for 363 (15.5%) of those randomised, of whom 102 (4%) had pre-eclampsia: 179 (15.3%) intervention group and 184 (15.7%) usual care [Table 2]. The primary outcome (time to clinic hypertension defined from the clinical records) was not significantly different between individuals who self-monitored or received usual prenatal care alone (mean 104.3 days vs 106.2 days respectively, mean difference -1.6 days (95% confidence interval -8.1, 4.9; p = 0.6)) [Table 2]. This was not materially affected by sensitivity analyses including adjustment for missingness, multiple imputation or when clinic hypertension was restricted to evidence of raised professionally recorded BP only (i.e. recorded diagnosis of gestational hypertension or prescription

of anti-hypertensive medications alone was excluded) [eTable 2 in Supplement 3]. The primary outcome was not significantly different between randomised groups in most pre-specified subgroups including aspirin eligibility, gestational age at recruitment, parity, previous experience of self-monitoring, deprivation score, educational qualifications [eTable 3 and eFigure 1 and 2 in Supplement 3]. There was a significant interaction for ethnicity but both individual group results crossed unity.

Secondary Outcomes

Maternal outcomes

There was no statistically significant difference in the incidence of severe hypertension or in the incidence of pre-eclampsia between the groups [Table 3].

The incidence of serious maternal complications was 15/1209 (1.2%) of those in the self-monitoring group and 19/1209 (1.6%) of those receiving usual care; the pre-specified threshold of sufficient events to undertake a formal statistical comparison was not met (2% or more) [Table 3]. No participants in either group died.

There was no significant difference in the proportion with spontaneous onset of labour (482/1187, 41% self-monitoring vs 493/1181, 42% usual care; adjusted relative risk 0.97 (0.9, 1.1). Indications for induction or pre-labour caesarean section are presented in eTable 4.

Anxiety (STAI6),[20] was not significantly different between groups at either 30 weeks' gestation or postnatally [eTable 6 in Supplement 3]. Individuals in the self-monitoring group had significantly improved scores on the modified brief Illness Perception Questionnaire at both 30 weeks and postnatally [eTable 7 in Supplement 3].[19] Participants' health-related quality of life based on index scores derived from the EQ-5D-5L descriptive system[21] was not significantly different between groups at 30 weeks or at postnatal follow-up [eTable 8 in Supplement 3].

Perinatal Outcomes

The proportions of stillbirths and early neonatal deaths in both groups were not formally compared due to low rates of occurrence. [Table 3]. Mean birthweight was 3247g in the self-monitoring group and 3264g for usual care. Small for gestational age infant birthweight (<10th centile) was present in 104/1249 (8.3%) self-monitoring vs 87/1235 (7.0%) usual care; adjusted relative risk 1.2 (0.9, 1.5) Median gestation at delivery was not different between groups (39 weeks) [Table 3]. There were no significant differences in the proportions of either randomised groups that were admitted to a neonatal unit or for subsequent length of stay [Table 3 and eTable 5]. Spontaneous vaginal delivery occurred for (550 (43.7%) self-monitoring participants vs 527 (42.4%) usual care [eTable 5 in Supplement 3].

Adverse events

Eighteen serious adverse events were reported during the trial with none judged as related to the intervention by the supervising site principal investigator: 12 (1%) in the self-monitoring group (2 miscarriages 20-23^{+6}/40, 5 still births, 2 neonatal deaths, 3 terminations for fetal abnormalities) and 6 (0.5%) in those receiving usual care (3 still births, 3 terminations due to fetal abnormalities (2) and sepsis (1)).

Post hoc outcomes

In a post hoc analysis, fidelity to the intervention by individuals randomised to self-monitoring was explored. Of the 1220 allocated to self-monitoring appropriately, 1198 self-monitored and 22 did not. The vast majority of participants used the app (1196, 99.8%) with 23 (2.2%) also recording some readings in a paper diary and 2 (0.2%) exclusively using a paper diary. Because data in the paper diaries were not directly comparable to that in the App (for example in terms of recording of timing

of readings, repeat readings), those readings were excluded from further analysis. Participants followed the protocol of monitoring three times per week until delivery or clinic hypertension 76.7% of the time; if their SMBP rose to ≥135/85mmHg and they were asked to monitor daily until delivery or hypertension diagnosis, this happened 71.7% of the time.

Of the 179 individuals with clinic hypertension in the intervention group, 131 (73%) had self-monitored within a week of that diagnosis and 16 (9%) had no self-monitored readings at all [Table 4]. Of these, 109/179 (61%) individuals had a raised SMBP ≥140/90mmHg on the same day or before the detection of clinic hypertension. The median time between first raised SMBP and a subsequent diagnosis of hypertension was 29 days (interquartile range 7 to 72). Of those with a clinic diagnosis of hypertension, 43/179 (24%) did not have a raised SMBP (indicating likely white coat hypertension) at or before that time [Table 4].

DISCUSSION

In this randomized trial, SMBP from 20 weeks' gestation until delivery or development of hypertension, in addition to usual care, did not lead to an earlier diagnosis of clinic hypertension, defined on the basis of routinely recorded clinical data. There were no significant differences in either maternal or perinatal outcomes or of serious adverse events. Of those individuals who self-monitored BP in the trial who received a diagnosis of hypertension, the majority had self-monitored within a week of diagnosis suggesting that these individuals would have had an opportunity to detect hypertension at home.

To our knowledge, this was the largest randomised clinical trolled trial of blood pressure self-monitoring in individuals with higher-risk pregnancy published to date and was powered to detect

clinically important differences between the groups.[24] The pragmatic trial design and broad inclusion criteria make findings applicable to routine antenatal care. Participants randomised had appropriate representation of ethnic minority ethnic groups but there was some evidence of over representation of those with higher educational attainment in the trial overall. Follow-up was high with over 95% of the primary outcome data available.

A recent systematic review found two randomised clinical trials involving self-monitoring in antenatal care, one of which used self-monitoring as a screening test[10]: one UK-based group randomised 80 low risk pregnant individuals to weekly self-monitoring with reduced routine antenatal clinics and found that for individuals who self-monitored, overall clinic attendance was reduced despite an increase in unscheduled care.[25] A French group randomised 57 individuals with pregnancy hypertension without proteinuria between 18-36 weeks to self-monitor BP with or without transmission of the measurements to their supervising clinicians and found no significant difference between groups.[26] More recently, a US group randomised 300 low risk pregnant individuals to remote monitoring with reduced clinics vs usual care. The individuals randomised to remote care had reduced obstetric input but more nurse/midwife time was needed for providing remote care.[11] Two other subsequent trials were not comparable.[27 28] Two ongoing self-monitoring trials, one in high risk pregnancies and one with a similar screening strategy to the current study have not reported yet.[29,30]

Self-monitoring of BP outside of pregnancy is already widespread and has a strong evidence base.[7,8,31] Prior to the current study there were few data regarding the prevalence of SMBP in pregnancy, although the CHIPS study of different BP targets in pregnancy hypertension reported 38% of hypertensive pregnant individuals as self-monitoring.[32] A survey undertaken in parallel to this trial, but excluding those randomised found that in a sample of around 5500 pregnant individuals, 17% of those without hypertension and 49% of those with hypertension were self-monitoring, often without clinician involvement.[33]

Limitations

The study has several limitations. First, the trial was powered to detect a 12-day earlier presentation with SMBP compared to clinic-based diagnosis, a difference that was considered to be clinically relevant. Although very small differences cannot be ruled out, self-monitoring did not result in a clinically important or statistically significant earlier presentation of hypertension. Second, the study was not powered to detect differences in clinical outcomes. Third, the home readings for 26% of individuals with a clinic-based primary outcome of hypertension were normal, so that these participants could not have presented earlier on the basis of self-monitoring. Data on prognosis of white coat hypertension remains sparse, particularly as to the relative effect of antihypertensive therapy compared to true hypertension and therefore appropriate management strategies are uncertain.[34]

Fourth, 61% of those with hypertension in the intervention group had elevated home BP prior to or concurrently with clinic BP and for these participants, SMBP rose approximately one month prior to their clinic recorded hypertension. Participants received advice through the app to check such readings with a midwife but there were no data regarding the response of participants and/or clinicians to such readings. Linked qualitative work suggested that clinicians tend to favor clinic readings in the case of discordance, perhaps explaining the observed lack of effect on the primary outcome.[35]

Fifth, 27% of randomised individuals had self-monitored prior to randomisation which might have diluted any effect from the intervention. The study did not collect data regarding whether self-monitoring continued later in pregnancy. However, other research suggests that at least half of these participants may have continued to do self-monitoring without the knowledge of their clinical team.[33] Outside of pregnancy, there is evidence that such monitoring (without clinical support) has little effect on blood pressure.[8,33]

Sixth, the threshold for hypertension diagnosis with SMBP in pregnancy is not established. In the current study, the same BP threshold was used for home and clinic BP (140/90mmHg), although participants were asked to increase the frequency of measurement once their pressure reached 135/85mmHg. This choice was made on the basis of a systematic review of BP measurement in different settings, which suggested that self- and clinic monitored BP were equivalent in normotensive pregnant individuals; it was also influenced by concerns from clinicians during the development phase regarding over alerting.[13,17] A lower threshold for home readings might have led to a different result.

Conclusions

Among pregnant individuals at higher risk of pre-eclampsia, blood pressure self-monitoring with telemonitoring compared with usual care did not lead to significantly earlier clinic-based detection of hypertension.

Figures and Tables

Table 1: Baseline characteristics

Table 2: Primary Outcome

Table 3: Maternal and perinatal outcomes

Table 4: Self-monitoring vs clinic blood pressure for diagnosis of raised blood pressure

Figure 1: Flow through the trial

Eligibility, randomization, and data availability in a trial of self-monitoring for hypertension in pregnant individuals at risk for pre-eclampsia.

Supplemental Content

Supplement 1 Trial Protocol

Supplement 2 Statistical Analysis Plan

Supplement 3 Supplementary tables and figures

Supplement 4 The BUMP investigators

Supplement 5 Data sharing statement

Authors' contributions

RM together with LC and KT, conceived and led the study, providing detailed supervision of all aspects throughout. RM and LC contributed equally. LMY, LH, ORA, CC, MG, SG, JH, PL, CM, LM, JS, LT and LY provided senior expertise and leadership, contributing to designing the study, securing funding and supervising the conduct of the study. HW and CC led the research midwifery team with LL. LMY with SM, carried out the statistical analysis, and HC and ORA carried out the economic analysis. LY, LT and LH led the development of the intervention and supported its implementation with CV and MS. MF and GD with LE led trial implementation supervised by JA. MG was the key public contributor. RM wrote the first draft with KT, LC and LMY. All authors commented on drafts of this paper. RM will act as guarantor and affirms that the manuscript is an honest, accurate, transparent, and full account of this trial. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of interests

RM has previously received BP monitors from Omron Healthcare for research purposes and is working with them on a telemonitoring system. LT is a Non-Executive Director & Director of R&D for Sensyne Health Plc. LM is a part-time employee and shareholder of Sensyne Health plc. ORA is a member of the Euroquol Group. All other authors declare no conflicts of interest.

The BP monitors for the trial were purchased from the manufacturer (Microlife) at commercial prices. The BUMP app has been developed into a commercial product in collaboration with Sensyne Health and provided free to the NHS during the coronavirus pandemic through free licencing from both University of Oxford and Sensyne Health.

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Role of the funder

The funders and sponsors of the study had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Access to data statement

Mr. SM and Dr. LMY had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis .

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Group Information: The BUMP Investigators are listed in Supplement 4.

Data sharing Statement: See supplement 5

References

1. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol.* 2013;170(1):1-7.
2. Wang W, Xie X, Yuan T, et al. Epidemiological trends of maternal hypertensive disorders of pregnancy at the global, regional, and national levels: a population-based study. *BMC pregnancy and childbirth.* 2021;21(1):364.
3. Cantwell R, Clutton-Brock T, Cooper G, 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 and gynaecology.* 2011;118 Suppl 1:1-203.
4. Knight MB, K.;Tuffnell, D.;Shakespeare, J.;Kotnis, R.;Kenyon, S.;Kurinczuk, J.J. ;. *Saving Lives, Improving Mothers' Care - Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2016-18.* Oxford: University of Oxford;2020.
5. NICE. Hypertension in pregnancy: diagnosis and management (NICE Guideline 107). National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/cg107. Published 2010. Accessed February 8, 2022.
6. Douglas KA, Redman CW. Eclampsia in the United Kingdom. *BMJ.* 1994;309(6966):1395-1400.
7. Hodgkinson JA, Lee MM, Milner S, et al. Accuracy of blood-pressure monitors owned by patients with hypertension (ACCU-RATE study): a cross-sectional, observational study in central England. *Br J Gen Pract.* 2020;70(697):e548-e554.
8. Tucker KL, Sheppard JP, Stevens R, et al. Self-monitoring of blood pressure in hypertension: A systematic review and individual patient data meta-analysis. *PLoS Med.* 2017;14(9):e1002389.
9. Constanti M, Boffa R, Floyd CN, Wierzbicki AS, McManus RJ, Glover M. Options for the diagnosis of high blood pressure in primary care: a systematic review and economic model. *J Hum Hypertens.* 2021;**35**, 455–461
10. Kalafat E, Benlioglu C, Thilaganathan B, Khalil A. Home blood pressure monitoring in the antenatal and postpartum period: A systematic review meta-analysis. *Pregnancy Hypertens.* 2020;19:44-51.
11. Butler Tobah YS, LeBlanc A, Branda ME, et al. Randomized comparison of a reduced-visit prenatal care model enhanced with remote monitoring. *Am J Obstet Gynecol.* 2019;221(6):638 e631-638 e638.
12. Hinton L, Tucker KL, Greenfield SM, et al. Blood pressure self-monitoring in pregnancy (BuMP) feasibility study; a qualitative analysis of women's experiences of self-monitoring. *BMC pregnancy and childbirth.* 2017;17(1):427.
13. Tucker KL, Taylor KS, Crawford C, et al. Blood pressure self-monitoring in pregnancy: examining feasibility in a prospective cohort study. *BMC pregnancy and childbirth.* 2017;17(1):442.
14. Dougall G, Franssen M, Tucker KL, et al. Blood pressure monitoring in high-risk pregnancy to improve the detection and monitoring of hypertension (the BUMP 1 and 2 trials): protocol for two linked randomised controlled trials. *BMJ Open.* 2020;10(1):e034593.
15. Band R, Hinton L, Tucker KL, et al. Intervention planning and modification of the BUMP intervention: a digital intervention for the early detection of raised blood pressure in pregnancy. *Pilot Feasibility Stud.* 2019;5:153.
16. 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):348-359.

17. Tucker KL, Bankhead C, Hodgkinson J, et al. How Do Home and Clinic Blood Pressure Readings Compare in Pregnancy? *Hypertension.* 2018;72(3):686-694.
18. NICE. Antenatal care for uncomplicated pregnancies (NICE Guideline 62). National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/cg62. Published 2008. Accessed February 8, 2022.
19. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. *J Psychosom Res.* 2006;60(6):631-637.
20. Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). *BrJClinPsychol.* 1992;31 (Pt 3):301-306.
21. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res.* 2011;20(10):1727-1736.
22. Ethnic group, national identity and religion. https://www.ons.gov.uk/methodology/classificationsandstandards/measuringequality/ethnicgroupnationalidentityandreligion. Accessed January 28, 2022.
23. Cragg JG. Some Statistical Models for Limited Dependent Variables with Application to the Demand for Durable Goods. *Econometrica.* 1971;39(5):829-844.
24. Tran K, Padwal R, Khan N, Wright MD, Chan WS. Home blood pressure monitoring in the diagnosis and treatment of hypertension in pregnancy: a systematic review and meta-analysis. *CMAJ Open.* 2021;9(2):E642-E650.
25. Ross-McGill H, Hewison J, Hirst J, et al. Antenatal home blood pressure monitoring: a pilot randomised controlled trial. *BJOG : an international journal of obstetrics and gynaecology.* 2000;107(2):217-221.
26. Denolle T, Weber JL, Calvez C, et al. Diagnosis of white coat hypertension in pregnant women with teletransmitted home blood pressure. *Hypertens Pregnancy.* 2008;27(3):305-313.
27. Pealing LM, Tucker KL, Mackillop LH, et al. A randomised controlled trial of blood pressure self-monitoring in the management of hypertensive pregnancy. OPTIMUM-BP: A feasibility trial. *Pregnancy Hypertens.* 2019;18:141-149.
28. Holm L, Stucke-Brander T, Wagner S, et al. Automated blood pressure self-measurement station compared to office blood pressure measurement for first trimester screening of pre-eclampsia. *Health Informatics J.* 2019;25(4):1815-1824.
29. van den Heuvel JFM, Ganzevoort W, De Haan-Jebbink JM, et al. HOspital care versus TELemonitoring in high-risk pregnancy (HOTEL): study protocol for a multicentre non-inferiority randomised controlled trial. *BMJ Open.* 2019;9(10):e031700.
30. Lanssens D, Thijs IM, Gyselaers W, consortium PI. Design of the Pregnancy REmote MOnitoring II study (PREMOM II): a multicenter, randomized controlled trial of remote monitoring for gestational hypertensive disorders. *BMC pregnancy and childbirth.* 2020;20(1):626.
31. McManus RJ, Mant J, Franssen M, et al. Efficacy of self-monitored blood pressure, with or without telemonitoring, for titration of antihypertensive medication (TASMINH4): an unmasked randomised controlled trial. *Lancet.* 2018;391(10124):949-959.
32. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med.* 2015;372(5):407-417.
33. Tucker KL, Hodgkinson J, Wilson HM, et al. Current prevalence of self-monitoring of blood pressure during pregnancy: the BUMP Survey. *J Hypertens.* 2021;39(5):994-1001.
34. Johnson S, Liu B, Kalafat E, Thilaganathan B, Khalil A. Maternal and Perinatal Outcomes of White Coat Hypertension During Pregnancy: A Systematic Review and Meta-Analysis. *Hypertension.* 2020;76(1):157-166.
35. Hinton L, Hodgkinson J, Tucker KL, et al. Exploring the potential for introducing home monitoring of blood pressure during pregnancy into maternity care: current views and experiences of staff-a qualitative study. *BMJ Open.* 2020;10(12):e037874.

564 36. Exploring the UK's Digital Divide. Office for National Statistics.
565 https://www.ons.gov.uk/peoplepopulationandcommunity/householdcharacteristics/homein
566 ternetandsocialmediausage/articles/exploringtheuksdigitaldivide/2019-03-04 Published
567 2019. Updated 04/03/2019. Accessed February 8, 2022.
568 37. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-
569 5D-5L to EQ-5D-3L value sets. *Value Health.* 2012;15(5):708-715.

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572 *Table 1: baseline characteristics by randomised group*

	Self-Monitoring	Usual Care
Characteristic	n=1220 [a]	n=1217 [a]
Age (years)	32.8 (5.7)	33.0 (5.6)
Gestation (weeks) at entry	20.3 (1.6)	20.3 (1.6)
Parity: no previous births	745 (61.1%)	742 (61.0%)
Body mass index (kg/m^2)	26.5 (22.7 to 32.1)	26.1 (22.6 to 32.4)
Index of multiple deprivation quintile [b]	n=1210	n=1211
1 (most deprived)	167 (13.8%)	170 (14.0%)
2	247 (20.4%)	239 (19.7%)
3	228 (18.8%)	258 (21.3%)
4	254 (21.0%)	244 (20.2%)
5 (least deprived)	314 (26.0%)	300 (24.8%)
Ethnicity [c]	n=1211	n=1007
Asian or Asian British	135 (11.1%)	118 (9.8%)
Black or Black British	88 (7.3%)	99 (8.2%)
Chinese	16 (1.3%)	11 (0.9%)
Mixed	55 (4.5%)	41 (3.4%)
Other	30 (2.5%)	24 (2.0%)
White (British, Irish, Other)	887 (73.3%)	914 (75.7%)
Current smoker	57 (4.7%)	59 (4.9%)
Highest education	n=1209	n=1201
Tertiary Education	715 (59.1%)	684 (57.0%)
Professional qualifications, n(%)	122 (10.1%)	120 (10.0%)
A-level or GCSE, n(%)	294 (24.3%)	335 (27.9%)
Vocational qualifications, n(%)	34 (2.8%)	32 (2.7%)
No formal qualifications, n(%)	44 (3.6%)	30 (2.5%)
Risk factors for hypertension		
Body mass index > 30 kg/m2	444 (46.4%)	417 (34.3%)
Previous hypertensive disorder of pregnancy	199 (16.3%)	220 (18.1%)
Family history of pre-eclampsia	144 (11.8%)	133 (10.9%)
Autoimmune disease[d]	83 (6.8%)	81 (6.7%)
Pre-pregnancy Diabetes (type 1 or 2)	75 (6.2%)	67 (5.5%)
Twin pregnancy	73 (6.0%)	67 (5.5%)
Interval between pregnancies >10 years	34 (2.8%)	36 (3.0%)
Chronic kidney disease (any grade)	9 (0.7%)	14 (1.2%)
Blood pressure [e]	n=1161	n=1162
Mean SBP at entry	113.4 (12.8)	113.9 (12.3)
Mean DBP at entry	68.5 (9.0	69.0 (9.0)
Health questionnaires	n=1202	n=1194
EQ-5D-5L Index Value[f]	0.88 (0.77 to 1.00)	0.85 (0.77 to 1.00)
	n=1201	n=1191
STAI-6[g]	22.2 (55.6 to 33.3)	22.2 (5.6 to 33.3)

Self-monitoring prior to trial N, n (%)	n=1209	n=1205
	305 (25%)	334 (28%)

Data are n (%) or mean (SD) or median (interquartile range).

SBP: systolic blood pressure; DBP diastolic blood pressure.

[a] As shown in Figure 1, 1223 (self-monitoring) and 1218 (control) were randomised, however 3 intervention and 1 control participant were randomised in error and withdrawn immediately hence data are presented here for the remaining 1220 and 1217 respectively. N as stated unless otherwise specified.

[b] The index of multiple deprivation is an assessment of deprivation based on a multiple weighted components including income, employment, education, health, crime, barriers to housing and services, and living environment. It is assessed at the postcode level.

[c] Ethnicity self-attributed from closed list based on standard UK classification. Mixed included those self-identifying as mixed ethnicity (any combination). Other included any other ethnicity not listed above in which case participants were asked to specify: Self-monitoring: Arab: 4, Japanese: 3, Latin American: 2, Mauritian: 2, Brazilian: 1, Filipino: 1, Iraqi Kurdish: 1, Pacific Islander: 1, Tibetan Burmese Origin: 1, Turkish Kurdish: 1, Vietnamese: 1, Middle Eastern: 1, None stated: 11.
Usual care arm: Latin American: 6, Arab: 3, Japanese: 2, Afghan: 1, Brazilian: 1, Filipino: 1, Iranian: 1, Malaysian: 1, South East Asia: 1, South Korean: 1, Vietnamese: 1, None stated: 5.

[d] Any autoimmune disease for example systemic lupus erythematosis or antiphospholipid syndrome

[e] at last clinic visit prior to randomisation

[f] EQ-5D-5L: EuroQol instrument 5 Dimensions 5 levels (index value calculated from 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Value calculated using cross walk tool[37] range -0.3-1, higher is better quality of life).

[g] STAI: short form of stait-trait anxiety inventory (6 items range 6-24; scaled to be out of 100, higher is more anxious).[20]

598 Table 2: Primary outcome: time from randomisation to diagnosis of raised sustained blood pressure

	Self-Monitoring	Usual Care	Estimated effect [95% CI]	P value[b]
Participants with primary outcome data	1171	1175		
Clinic hypertension[a]	179 (15.3%)	184 (15.7%)	0.0% [-3% to 2%][c]	0.75
Mean time to clinic hypertension (days)	104.3 (32.6) [n=179]	106.2 (32.0) [n=184]	-1.6 [-8.1 to 4.9][d]	0.64
Median (interquartile range)	109 (90 to 127) [n=179]	115 (90 to 129) [n=184]		

599

600 Data are n (%) or mean (SD).

601 [a] Sustained raised blood pressure defined as two blood pressures ≥140/90mmHg within 168 hours or a
602 recorded diagnosis of pregnancy hypertension or prescription of an antihypertensive medication, whichever
603 came first.

604 [b] Self-monitoring versus usual care: threshold level of significance p = 0.05.

605 [c] Difference in percentage of having raised blood pressure modelled against randomised group, parity, and
606 site.

607 [d] Mean difference in days to clinic hypertension

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612 Table 3 Selected Secondary Maternal and Perinatal Outcomes by Randomised Group [a]

	Self-Monitoring	Usual Care	Adjusted absolute difference (95% CI)[b]	Adjusted risk ratio[b] (95% CI)	P value for treatment effect
MATERNAL					
Severe hypertension	69/1171 (6.0%)	57/1175 (4.9%)	1.09% [-0.94% to 3.12%]	1.22 [0.87 to 1.70]	0.25
Pre-eclampsia (N)	51/1209 (4.2%)	51/1209 (4.2%)	0.01% [-1.84% to 1.85%]	1.00 [0.66 to 1.51]	1.00
One or more serious maternal complications [c]	15/1209 (1.2%)	19/1209 (1.6%)	--	--	--
PERINATAL					
Median Gestation at delivery (IQR)	39.3 (38.1 to 40.4) *N=1190*	39.3 (38.0 to 40.4) *N=1185*	0.14 [-0.01 to 0.30][d]	--	--
Stillbirth	5/1260 (0.4%)	3/1248 (0.2%)	--	--	--
Neonatal death within 7 days	2/1248 (0.2%)	*0/1240*	--	--	--
Small for gestational age (<10th centile)	104/1249 (8.3%)	87/1235 (7.0%)	1.10% [-1.09% to 3.29%]	1.15 [0.87 to 1.53]	0.32
Infant admitted to neonatal intensive care	161/1248 (12.9%)	163/1240 (13.1%)	-0.64% [-3.34% to 2.05%]	0.95 [0.77 to 1.17]	0.63

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614 [a] See tables e3 and e4 in Supplement 3 for additional maternal and perinatal outcomes

615 [b] Statistical comparisons completed when >2% event rate: Self-monitoring versus usual care. Log-Poisson generalised linear mixed effects model with
616 robust standard errors adjusted for randomised arm, and parity as fixed effects; and site as a random effect. Level of significance p<0.05

617 [C] one or more from: Eclampsia, transient ischemic attack or stroke, HELLP syndrome (haemolysis, elevated liver enzymes, low platelets), liver involvement
618 (ALT or AST >70 U/L), pulmonary oedema, renal involvement (creatinine≥90mmol), haematological involvement (platelets <x100^9/L).
619 [d] Estimated median difference (95% confidence interval) derived from quantile regression adjusted for randomised arm, parity and site.
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Table 4: Self-monitoring vs clinic blood pressure for diagnosis of raised blood pressure

		Raised BP on any home readings[b]		
		Yes	No	Total
Raised BP on any health professional readings[a]	Yes	120	43	163
	No	240	651	891
	Total	360	694	1054

This table includes all 1054 women randomised to self-monitoring who had both health professional and self-monitored blood pressures recorded

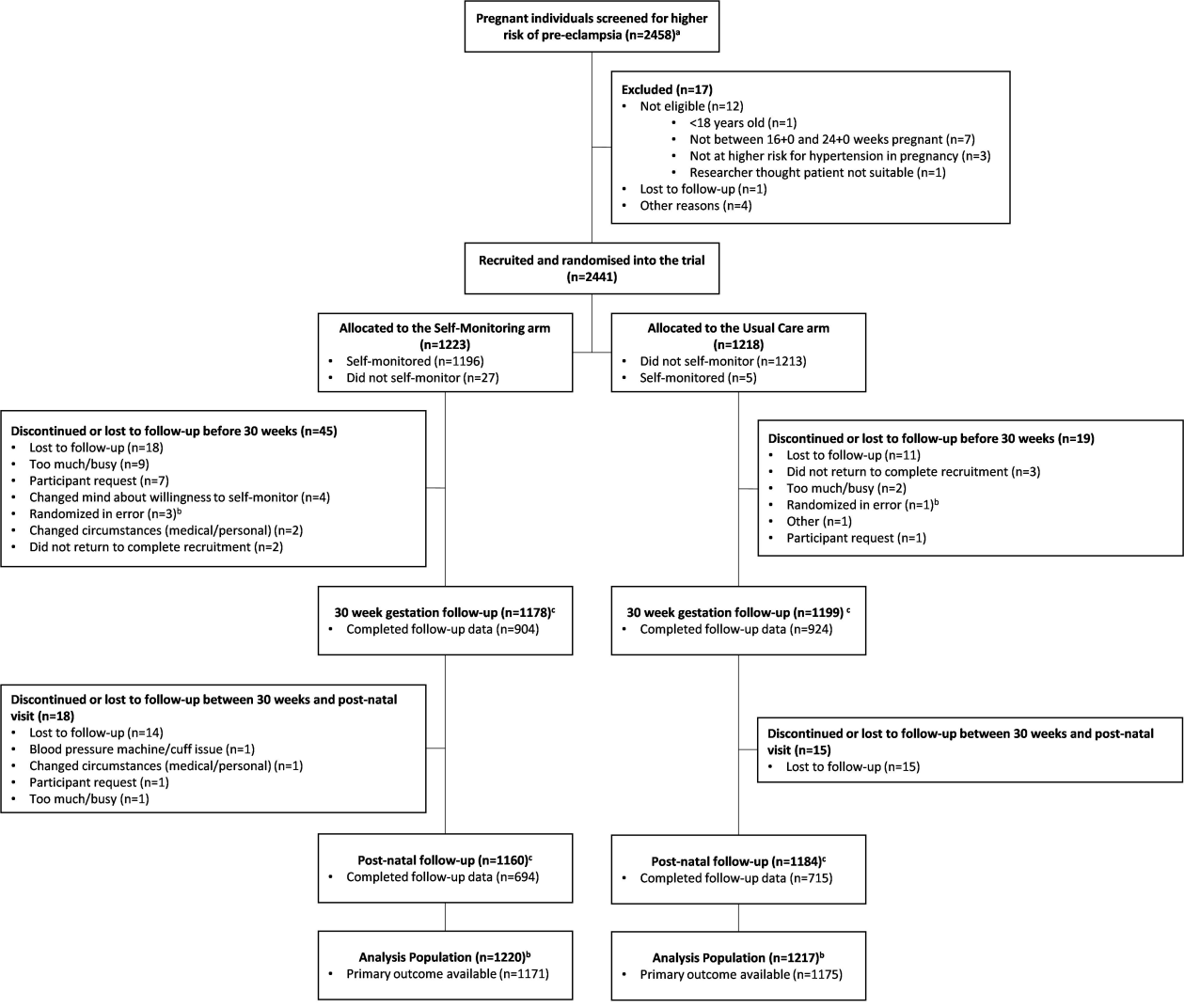
163 (15.5%) had clinic hypertension

43 (4.1%) had white coat hypertension (raised in clinic but not at home)

240 (22.8%) had masked hypertension (raised at home but not in clinic)

[a]Two blood pressures ≥140/90mmHg from any community or hospital setting within 168 hours or a new prescription of antihypertensive medication for raised blood pressure, whichever came first.

[b]First recording of ≥140/90mmHg on home blood pressure device.



[a] Pregnant individuals that were screened for higher risk of pre-eclampsia were selected as potentially suitable by research midwives reviewing clinical notes, and so may under-represent the true number of potential participants. 'Higher risk of pre-eclampsia' was defined by the relevant UK guidance at the time and included one or more of the following risk factors for pregnancy hypertension[5]: age ≥40 years nulliparity pregnancy interval >10 years, family history pre-eclampsia, previous history pre-eclampsia or gestational hypertension, body mass index ≥30 kg/m^2, chronic kidney disease (any CKD stage), twin pregnancy, pre-pregnancy diabetes, autoimmune disease (for example systemic lupus erythematosus or antiphospholipid syndrome).

[b] Four individuals were randomized in error (three in the self-monitoring arm and one in the usual care arm) and were excluded from the analysis population

[c] The follow-up numbers represent firstly those individuals eligible to be followed-up (i.e. not withdrawn or lost to follow-up) and secondly those completing questionnaires at that time point

All available data were included in the analyses but some were available at only one follow-up point:

For the self-monitoring arm 615 participants completed both 30 weeks and post-natal follow-up. 289 participants completed only 30 weeks follow-up. 79 participants completed only post-natal follow-up. 240 participants completed neither follow-up.

For the usual care arm 636 participants completed both 30 weeks and post-natal follow-up. 288 participants completed only 30 weeks follow-up. 79 participants completed only post-natal follow-up. 215 participants completed neither follow-up.