Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

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1. Inclusion Criteria

i. Women with either a new or a known diagnosis of chronic hypertension (CHTN) during pregnancy receiving prenatal care at participating centers were eligible for screening:

First, a diagnosis of CHTN was verified as follows:

- New CHTN: This required elevated SBP ≥140 and/or DBP≥ 90 mm Hg on two occasions at least four hours apart prior to 20 weeks' gestation in a patient who had never received a diagnosis of CHTN and antihypertensive therapy (including lifestyle measures). The BPs on the day of screening counted towards confirming the diagnosis as well as towards entry BP criteria.
- Known CHTN: Documented prior diagnosis and prescription of antihypertensive therapy (including lifestyle) for BP control confirmed the diagnosis of known CHTN during pregnancy. These patients had to meet BP requirements at randomization.

Review of records was required for all patients to exclude severe hypertension and other criteria.

Next, entry BP based on the clinic BP depended on whether the patient was currently on antihypertensive therapy and adherent:

- If new/untreated or not adherent with monotherapy (i.e. had not taken medication within 24 hours of randomization): Clinic BP at randomization must be within the range of 140-159 systolic or 90-104 diastolic. The clinic BP was based on the usual clinic BP used for decision-making: the single BP if <140/90, and the second BP if ≥140/90 and repeated.

  ***Patients with diastolic BP in the upper range of mild CHTN (105-109) were excluded – as more providers may treat patients at these upper BP ranges. Excluding the upper range of mild CHTN provided a buffer to protect protocol adherence.*
- If known CHTN and adherent with monotherapy within the previous 24 hours (including combination agents in a single tablet): BP at randomization must be SBP <160 and DBP<105 (including those with BP<140/90). This was consistent with standard ACOG definitions of CHTN in pregnancy and management recommendations.

**Note, patients on monotherapy who were not adherent (had not taken medication within 24 hours of randomization) were considered untreated and the thresholds for untreated CHTN (140-159/90-104 per protocol) applied.

- Clinic BP used for entry into the study and management was based on pragmatic clinic BP measurements according to CHAP MOP (see measurement details below). Clinical personnel at all sites were in-serviced on the BP measurement protocol and all research staff were trained and certified on measurement and management protocol.

ii. Singleton (twins reduced to singleton or with vanishing twin syndrome prior to 14 weeks qualified)

iii. Viable pregnancy <$23^{0/7}$ weeks of gestation (without preeclampsia / or gestational hypertension). For those with a history of chronic hypertension randomized between 20-$22^{6/7}$, documentation of urine protein <+1 on dipstick OR <0.3 on protein/creatinine ratio OR <300 mg/24 hours on the date of randomization was required to rule out preeclampsia. In women who had no history of chronic hypertension, at least 2 blood pressures ≥140/90 prior to 20 weeks distinguished from gestational hypertension. ***Gestational age determination:*** *ACOG criteria (most recent) with ultrasound required prior to randomization*

2. Exclusion criteria

i. Clinic BPs at randomization confirmed ≥160 systolic or ≥105 diastolic (with or without treatment).

ii. Established history of severe hypertension e.g. a) Patients currently treated with >1 antihypertensive medication (more likely to have severe CHTN). Those on a combination medication in a single pill should not be excluded; b) A diagnosis of severe hypertension by clinical provider after review of BPs to confirm ≥160/110. ** Of note, severe BP elevations due to antepartum or postpartum preeclampsia or gestational hypertension in a *prior* pregnancy or isolated during stress should not be used to include or exclude patients in CHAP.

iii. Multifetal pregnancy (since are they at increased risk for key outcomes)

iv. Known history of or diagnosis of secondary cause of CHTN

v. High-risk co-morbidities for which treatment may be indicated:

- Diabetes mellitus diagnosed at age ≤10 years or duration of diagnosis ≥20 years
- Diabetes mellitus complicated by end organ damage (retinopathy, nephropathy, heart disease, transplant)
- Chronic kidney disease - including baseline proteinuria (>300mg/24-hr, protein/creatinine ratio >0.3, or persistent 1+ proteinuria*) or creatinine >1.2.

  *If a dipstick value at screening is more than trace, a clean catch or catheter urine should be obtained and re-tested by dipstick. If this shows trace or absence of protein, the patient is included. If it again shows 1+ protein, the patient is excluded until a 24-hr urine <300mg/24hr or p/c ratio is <0.3. If a p/c ratio is >0.3, the patient may be included if a 24-hour urine is < 300 mg.
- Cardiac disorders: cardiomyopathy, angina, CAD
- Prior stroke
- Retinopathy
- Sickle cell disease

vi. Known major fetal anomaly in current pregnancy

vii. Known fetal demise in current pregnancy

viii. Suspected IUGR

ix. Membrane rupture or planned termination prior to randomization

x. Plan to deliver outside the consortium centers (unless approved by the Clinical Coordinating Center) or unlikely to follow-up in the opinion of study staff or participation in this trial in a previous pregnancy

xi. Contraindication to labetalol and nifedipine (e.g. know hypersensitivity)

xii. Current substance abuse or addiction (cocaine, methamphetamine)

xiii. Participation in another trial without prior approval (CHAP participants were not enrolled in other trials without prior approval by protocol committee)

xiv. Physician or provider refusal

xv. Patient refusal

3. BP Measurement

i. <u>Training and certification of Staff and Centers</u>: Training of staff and pilot testing of procedures were crucial to standardized study procedures including accurate and reproducible BP measurement, quality control and data quality. Two different training models were used: central training for study staff and the train-the-trainer approach. For central training, all relevant research staff members from all clinical sites were administered training. Ongoing training was provided to new team members and refresher training regularly throughout the study.

In the train-the-trainer aspect, the research staff at each clinical center with the assistance of the clinical and data coordinating center as needed, provided training sessions and video training for clinical staff charged with measuring patients' BP and following the treatment algorithms of the study protocol. In addition, they organized training and refresher training sessions, as needed, including any remedial training in specific areas targeted by quality control monitoring for a specific site.

Clinical site approval to enroll and randomize participants was dependent upon completion of a series of preliminary tasks: submission of a site implementation plan that was reviewed and approved by the coordinating center; regulatory approvals (IRBs); completion of site staff training and certification; and receipt study supplies (including medications, Omron BP devices, etcs). Site visits were undertaken by the coordinating centers to ensure study enrollment/randomization followed proper study procedures. A training manual and video instruction supplemented the protocol.

ii. Measurement Procedures

Accurate measurement of blood pressure was critical to the conduct of the CHAP study. This section outlines instructions for the pragmatic, accurate and reproducible measurement of BP at the screening/enrollment visits and during subsequent antepartum and postpartum clinic visits. These were used for study entry and management of medication changes. Although oversight provided by research staff during clinic measurements was routinely available when participants were admitted to the hospital or presented to an emergency unit. The blood pressures measured during those encounters were also collected and used to adjudicate key study outcomes including preeclampsia.

A standard automated blood pressure measurement device (the OMRON HEM-907 XL Professional Digital Blood Pressure Monitor) and a specific protocol for the measurement of blood pressure was utilized at the randomization visit and this was blinded to clinical providers for ancillary research use (unless the measure was designated as the pragmatic clinic BP for management purposes in the absence of another device).

- When obtaining blood pressures for eligibility and clinical decision making, an automated (including the OMRON if the only device available) or a manual BP device was used.
- The clinical staff at each site were in-serviced on the following aspects of blood pressure measurement using the usual clinic BP device and standard procedure in the manual:
  1) Appropriate patient positioning
  2) Correct cuff size
  3) Appropriate waiting period of 5 minutes of rest prior to taking blood pressure
  4) Repeating blood pressure 1 time after the initial measure if SBP≥140 and/or DBP≥90.
  5) The repeat pragmatic BP was the BP used for randomization and clinical decision making at follow-up visits. If <140/90 the single BP was considered the BP of the day for enrollment or management.
  6) Blood pressure measured early in the visit after a 5 minute period of rest and before stressful procedures (e.g. blood draw).
- The techniques for obtaining seated blood pressure included applying the blood pressure cuff and placing the midpoint of the length of the bladder over the brachial artery and the mid-height of the cuff at heart level:
  - Lower edge of the cuff should be about 1 inch above the crease of the inner aspect of the elbow.
  - Wrap the cuff snugly and secure firmly.
  - The participant should rest with their palm turned upward.
  - The participant should be allowed to sit quietly for 5 minutes.
  - She should be seated comfortably, feet flat on the floor with her back supported.
  - Ideally should not have smoked or had caffeine within 30 minutes prior to the blood pressure check.

For an automated device run the BP and obtain document the readings

For a manual device:

Insert the earpiece of the stethoscope into ears.

Apply end-piece of stethoscope over the brachial artery, just below, but not touching, the cuff or tubing.

Close the bulb thumb valve and inflate the cuff at a rapid, but smooth, continuous rate to the maximum inflation pressure. The examiner's eyes should be level with the mid-range of the manometer scale and focused at the maximum inflation pressure.

Manipulating the thumb valve and maintain a constant rate of deflation (2 to 3 mm/Hg per second).

Korotkoff sounds become audible over the artery below the cuff and pass through four phases as the pressure declines and sounds disappear. The muffling and disappearance are referred to as the 4th and 5th phases:

Phase 1 (K1) – First appearance of faint, clear "tapping" sounds that increase in intensity (Corresponds to SBP – see below).

Phase 2 (K2) – A murmur or "swishing" quality is heard.

Phase 3 (K3) - Sounds are crisper and increase in intensity.

Phase 4 (K4) – Distinct, abrupt muffling of sounds - soft, "blowing" quality is heard.

Phase 5 (K5) – Sounds disappear (corresponds to DBP unless sound does not disappear).

The SBP is marked by the point at which the initial "tapping" sound is heard (K1).

"Muffling" occurs when the crisp Korotkoff sounds change (sudden diminution of sound) – 4th phase.

The fifth phase, when sounds become inaudible, is the best index of DBP.

*Strategies and tips to address variant patterns were addressed in the study manual of procedures.

Example of appropriate cuff sizes based on Measured Arm Circumference:

Arm Circumference	Cuff Size
< 22 cm (7 to 9")	Small
≥22 to <32 cm (9 to 13")	Medium
≥32 to <42 cm (13 to 17")	Large
≥42 to 50 cm (17 to 20")	Extra Large

4. BP Management

a) **Medication dosing: Active Treatment arm**

Either first line medication (labetalol or nifedipine ER) was initiated based on the patient's medical history, patient's past experience with antihypertensive medications, and provider preference/expertise. *In rare instances, patients and/or providers preferred a medication of choice other than labetalol or nifedipine ER, this was allowed and patients were still eligible for trial participation.*

The starting dose and escalation of therapy, supplied by the study, in the active treatment were as follows

<u>*Labetalol*</u>:

Started at 200 mg bid OR at the patient's current dose if on labetalol

Labetalol was escalated in increments of 200 mg bid to achieve blood pressures <140/90

Labetalol dose could be divided into tid dosing for symptoms suggesting intolerance including headaches, fatigue, hypotension with high doses or uncontrolled hypertension etc.

The maximum dose of labetalol was 2400 mg/day (1200 mg bid or 800 mg tid)

If the maximum tolerated dose of labetalol was reached, nifedipine ER was started. If nifedipine ER was contraindicated, or the patient was already on a maximum dose of nifedipine ER, a third line agent such as methyldopa was initiated.

<u>*Nifedipine ER*</u>:

Was started at 30 mg Qday or at the patient's current dose if currently on nifedipine ER. The ER pill should not be divided

Nifedipine ER was escalated in increments of 30 mg Qday to achieve blood pressures <140/90

Nifedipine dose was divided into bid dosing for symptoms, hypotension with high doses, or hypertension between doses

The maximum dose of nifedipine ER was 120 mg/day or 60 mg bid

If the maximum dose of nifedipine ER was reached, labetalol was started. If labetalol was contraindicated, or the patient was already on a maximum dose of labetalol, a third line agent such as methyldopa was initiated.

b) **Medication Dosing: Standard Care (No Treatment) arm**

Blood pressure medication was initiated for clinic BPs SBP ≥160 or DBP ≥105. Either first line medication (labetalol or nifedipine ER supplied by the study) or provider preferred medication (not supplied by the study) was initiated based on the patient's medical history, patient's past experience with antihypertensive medications, and provider preference/expertise. The goal BP for usual care was SBP <160 and DBP <105.

Labetalol:

Labetalol was started at 100-200 mg bid.

Labetalol was escalated in increments of 100-200 mg bid to achieve blood pressures <160/105

Labetalol dose could be divided into tid dosing for symptoms of fatigue, hypotension with high doses or hypertension between doses

The maximum dose of labetalol was 2400 mg/day (1200 mg bid or 800 mg tid)

If the maximum tolerated dose of labetalol was reached, nifedipine ER may be started. If nifedipine ER was contraindicated, or the patient was already on a maximum tolerated dose of nifedipine ER, a third line agent such as methyldopa was initiated.

Nifedipine ER:

Started at 30 mg Qday

Nifedipine ER was escalated in increments of 30 mg Qday to achieve blood pressures <160/105

Nifedipine ER dose could be divided into bid dosing for symptoms, hypotension with high doses, or hypertension between doses

The maximum dose of nifedipine ER was 120 mg/day

If the maximum tolerated dose of nifedipine ER was reached, labetalol could be started. If labetalol was contraindicated, or the patient was already on a maximum dose of labetalol, a third line agent such as methyldopa was initiated (but not supplied by the study).

In general, teams were encouraged to split the labetalol dose to tid or nifedipine ER dose to bid at higher doses before adding another BP medication to control BP or before reducing dose or switching to another medication in response to side effects.

c. Adherence to antihypertensive medications

Adherence was assessed as follows:

- The clinical provider (with the help of certified study staff as applicable) assessed adherence according to usual clinical routine to determine whether the participant had been adherent within the past 24 hours. For example, "When was the last time you took your medication? "Do you take your medication every day?" The provider used this information to determine whether to titrate the BP medication dose(s) as clinically indicated.
- At clinic visits, when the patient required a medication refill, study staff conducted a pill count of the patient's study medication and recorded it. This could be used to estimate adherence.

d. Schedule of follow-up visits

Follow-up was according to clinical routine or at the discretion of the health care provider (every 1-4 weeks depending on gestational age and practices at site).

If a participant had not taken medication and was not at the appropriate BP target, adherence was encouraged, and the participant was asked to return for another BP check within a week, and the medication dose evaluated again. If a problem with adherence persisted, study staff notified the study PI for decision making and assistance (such participants were still to be followed)

Table S1. Outcome Definitions

Primary Efficacy Outcome	**Definition**
Fetal or neonatal death*	Neonatal death valuated up to 28 days postpartum. Fetal deaths occurring prior to delivery
Superimposed preeclampsia with severe features up to two weeks postpartum*	a) Worsening HTN ≥160/110 after 20 weeks' gestation and proteinuria OR (in the absence of proteinuria). b) Worsening HTN above prior baseline (≥140/90) AND [cerebral (including seizures or persistent headaches) or persistent visual symptoms OR thrombocytopenia <100,000 OR creatinine≥1.2 mg/dL (or doubling from baseline), OR 2-fold elevated liver enzymes or HELLP syndrome OR persistent right upper quadrant pain OR pulmonary edema (including oxygen desaturation <90% requiring treatment with diuretics and oxygen).
Placental abruption*	Greater than usual uterine bleeding in the absence of placenta previa or trauma (associated with contractions, non-reassuring fetal heart tones and/or clinical diagnosis of abruption) leading to delivery. Other cases of "abruption" will be collected but not included in the primary outcome.
Indicated PTB <35 weeks*	Preterm delivery <35 weeks due to maternal or fetal reason, not due to spontaneous preterm labor or membrane rupture
Safety Outcome SGA <10th percentile	Birth weight <10th percentile for the gestational age according to Duryea's curve In addition, birth weight <10th percentile for the gestational age according to Alexander's curve (Alexander's curve was the original reference for this study and later expanded to include Duryea's curve)
Secondary Outcomes	
Composite serious maternal morbidity*	• Death • Cardiomyopathy or heart failure: Clinical diagnosis supported by echocardiography with ejection fraction ≤40% • Stroke: Clinical diagnosis supported by neurologic deficit and confirmation by CT or MRI imaging • Encephalopathy: Clinical diagnosis in setting of altered mental status • MI or angina: Clinical diagnosis confirmed by abnormal cardiac biomarkers (CK-MB or Troponin) and at least one clinical evidence (symptoms >10 minutes, ECG changes indicative of new ischemia or imaging suggesting new loss of viable myocardium) • Pulmonary edema: Clinical diagnosis supported by X-ray or CT • ICU admission/intubation • Acute kidney injury: serum creatinine ≥1.2 unrelated to preeclampsia
Preterm birth	< 37 weeks' gestation Indicated preterm birth - not reported (warrants additional programming)
Composite of serious neonatal morbidities	Bronchopulmonary dysplasia, Retinopathy of prematurity, Necrotizing enterocolitis (NEC) and Intraventricular hemorrhage grade III/IV; all based on clinical diagnoses (supported by relevant tests/imaging) as documented in the NICU records
Timing of delivery outcomes	Not reported
Treatment adherence, 6 weeks postpartum	Not reported
Preeclampsia*	Any preeclampsia (severe features as above or mild)
Gestational hypertension	Not reported (not adjudicated and not typically used with chronic hypertension)
Systolic and diastolic BP	Clinic BPs – mean overall and mean over time

Severe hypertension	BP ≥160/110 mmHg requiring treatment and/or recurrent
Severe hypertension + primary composite	Not reported
HELLP	Must have evidence of hemolysis, elevated liver enzymes & low platelets. • Hemolysis: must have one of LDH ≥600, Total bilirubin >1.2 mg/dL, or Hemolytic anemia on a peripheral smear • Elevated liver enzymes: twice elevated for reference lab • Low platelets: <100,000
Cesarean delivery	Cesarean mode of delivery as documented in medical records
Blood transfusion	Transfusion of packed red blood cells or whole blood
Other newborn outcomes	• NICU admission and stay • Low birth weight (<2500g) • Ponderal index: birth weight*100/height^3 (grams/cm^3)) • Head circumference (cm) • Placental weight (g) • Hypoglycemia (<40mg/dl) • Bradycardia (heart rate <80/min in first 48 hours) • Hypotension (Clinical diagnosis and mean BP < gestational age in weeks in first 72 hours) • Respiratory distress syndrome • Transient tachypnea of newborn • Respiratory support: Use of O2 mask, NC, CPAP, or ventilator in NICU • Seizures • Hyperbilirubinemia (direct bilirubin >2.0 mg/dL or phototherapy) • 5-min Apgar score <7 • Suspected or proven sepsis: Suspected sepsis leading to diagnostic work-up as documented in medical records
Health care resource utilization	**Not reported** • Prenatal clinic/ER visits • Prenatal hospitalizations • Delivery hospital stay (maternal/newborn) • Postpartum unscheduled/ER visits

*These outcomes were centrally and blindly adjudicated. The other outcomes were based on information abstracted from medical records into CHAP forms by trained and certified research staff using clinical diagnoses and criteria defined above

Multiple Imputation Approach for Missing Outcomes

The primary analysis follows an intention-to-treat (ITT) approach of all individuals randomized to the two treatment groups, regardless of whether they adhered to their assigned treatment. For cases where the primary composite outcome was undetermined (for example, dropout prior to delivery), the primary analysis utilized multiple imputation for the primary outcome. Missing values were estimated using characteristics within each treatment group that may be predictive of the composite outcome. Specifically, logistic regression models were fit within treatment groups using baseline characteristics including diabetes status (yes/no), treatment status before enrollment (on BP meds vs. not on BP meds), maternal age, BMI at enrollment, and elevated BP at the first visit (SBP ≥ 150 and/or DBP ≥ 100). Multiple imputed data sets were developed (5 replicates). The primary analysis was conducted on each of the imputed complete data sets, using models that included all baseline characteristics involved in the imputation, and the final results were pooled.

Log-binomial regression was used to generate the adjusted relative risk (RR) and 95% confidence intervals (CIs) for all primary outcomes. In accordance with the Statistical Analysis Plan, the analysis was repeated using logistic regression to generate the adjusted odds ratio (OR) and 95% CIs.

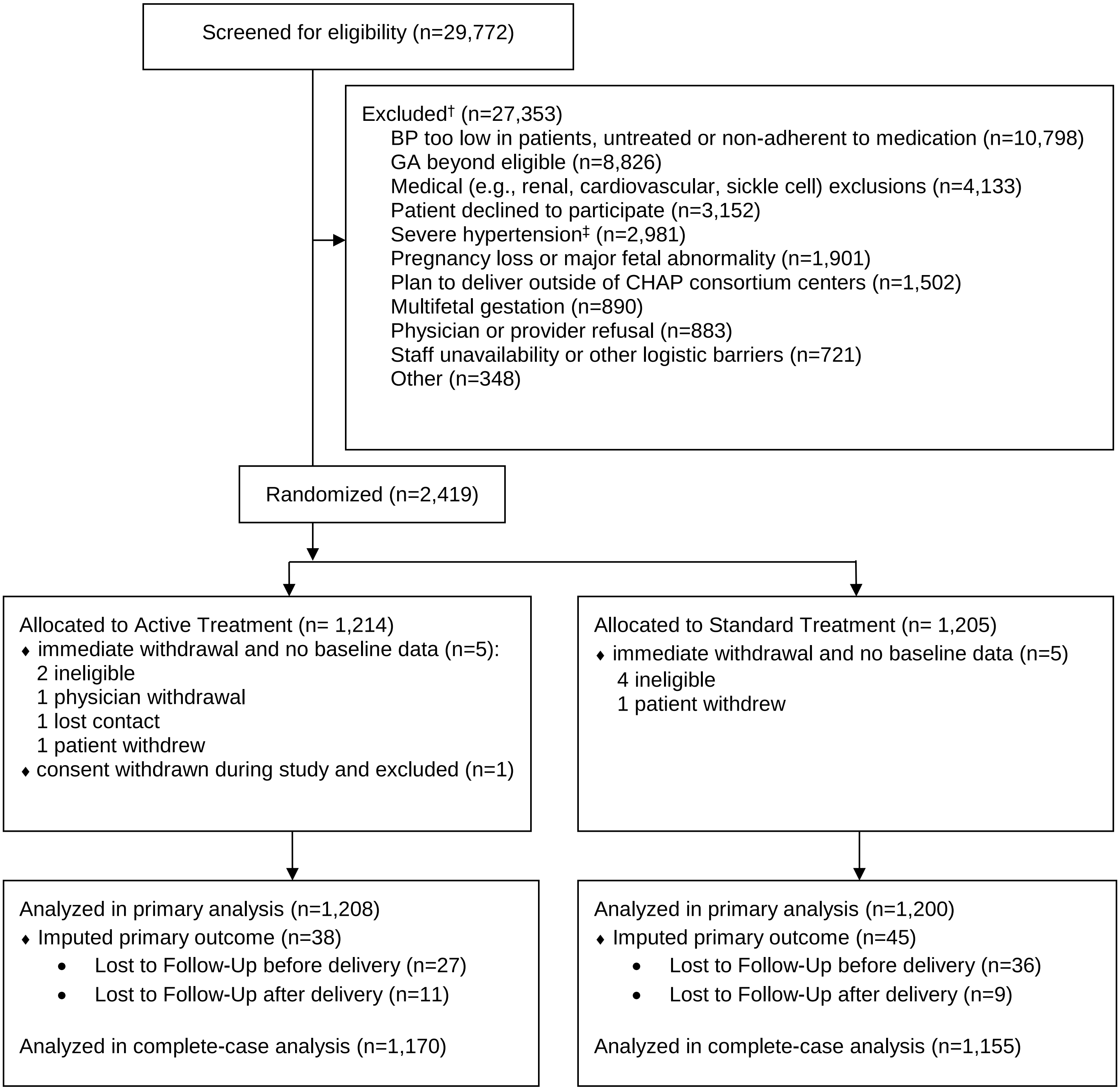
Sensitivity analyses included all individuals for whom a primary outcome could be assessed (a complete-case analysis) in a modified ITT approach. As expected, a small fraction (<10%) of the dataset required imputation and thus the complete case analyses agree substantially with the primary imputation-based analyses.

Additional Analysis Notes Regarding Test for Site Effect

We investigated whether there is a site effect with respect to the primary outcome. Using the complete case results and the Beslow-Day test there is no difference in effect by site (p=0.23) when treating each site separately. However, many sites have low enrollments and we performed an additional analysis where we combined sites with 25 or fewer enrolled into a single site. With this analysis, there again is no difference by site (p=0.08). With this configuration, there were 30 individual sites with enrollments greater than 25.

All analyses were conducted using SAS v9.4 (SAS Institute Inc., Cary, NC).

Figure S1. CONSORT diagram



† Screened patients may have more than 1 reason for exclusion.
‡ Severe hypertension category includes 1,098 with BPs above eligibility threshold on prior encounters, 1,056 taking more than 1 antihypertensive medication, 510 with average SBP exceeding eligibility threshold at final screen, and 290 with average DBP exceeding eligibility threshold at final screen.

Table S2. Antihypertensive use before randomization.

Antihypertensive	Active Treatment Group (n=1208)	Standard Treatment Group (n=1200)
Labetalol	383 (31.7%)	437 (36.4%)
Nifedipine	161 (13.3%)	137 (11.4%)
Almodipine	71 (5.9%)	74 (6.2%)
Methyldopa	63 (5.2%)	47 (3.9%)
HCTZ	56 (4.6%)	41 (3.4%)
Lisinopril	26 (2.2%)	25 (2.1%)
Metoprolol	21 (1.7%)	19 (1.6%)
Triamterene/HCTZ	3 (0.3%)	2 (0.2%)
Missing/Unknown	13 (1.1%)	19 (1.6%)
Other	28 (2.3%)	35 (2.9%)

Table S3. Active treatment drug assignment at randomization.

Antihypertensive	Active Treatment Group (n=1208)
Labetalol	745 (61.7%)
Nifedipine	430 (35.6%)
Almodipine	20 (1.7%)
Methyldopa	4 (0.3%)
HCTZ	3 (0.3%)
Other	2 (0.2%)

Table S4. Antihypertensive use at last blood pressure visit.

Antihypertensive	Active Treatment Group; On Meds (n=1047/1178)	Standard Treatment Group; On Meds (n=284/1163)	Active Treatment Group; Overall (n=1178)	Standard Treatment Group; Overall (n=1163)
Labetalol	662 (63.2%)	175 (61.6%)	662 (56.2%)	175 (15.1%)
Nifedipine	350 (33.4%)	87 (30.6%)	350 (29.7%)	87 (7.5%)
Almodipine	18 (1.7%)	5 (1.8%)	18 (1.5%)	5 (0.4%)
Methyldopa	5 (0.5%)	4 (1.4%)	5 (0.4%)	4 (0.3%)
HCTZ	3 (0.3%)	1 (0.4%)	3 (0.3%)	1 (0.1%)
Metoprolol	2 (0.2%)	4 (1.4%)	2 (0.2%)	4 (0.3%)
Other	2 (0.2%)	0 (0%)	2 (0.2%)	0 (0%)
Missing/Unknown	5 (0.5%)	8 (2.8%)	5 (0.4%)	8 (0.7%)
Not on Meds	-	-	131 (11.1%)	879 (75.6%)

Patients were considered to be on medications at their last visit if they answered "yes" to the question, "Is patient taking blood pressure medications." These could be either taking medications as prescribed or taking non-protocol medications. The table reflects the frequency of each designated antihypertensive medication for those considered to be on medications.

Columns 2-3 of table is restricted to those taking meds at the last visit. The distribution of those meds, by treatment group, are shown. A total of 1331 were on medications according to the last clinic visit from (out of a total 2341 with forms to review): 284/1163 (24.4%) in the Standard group and 1047/1178 (88.9%) in the Active group.

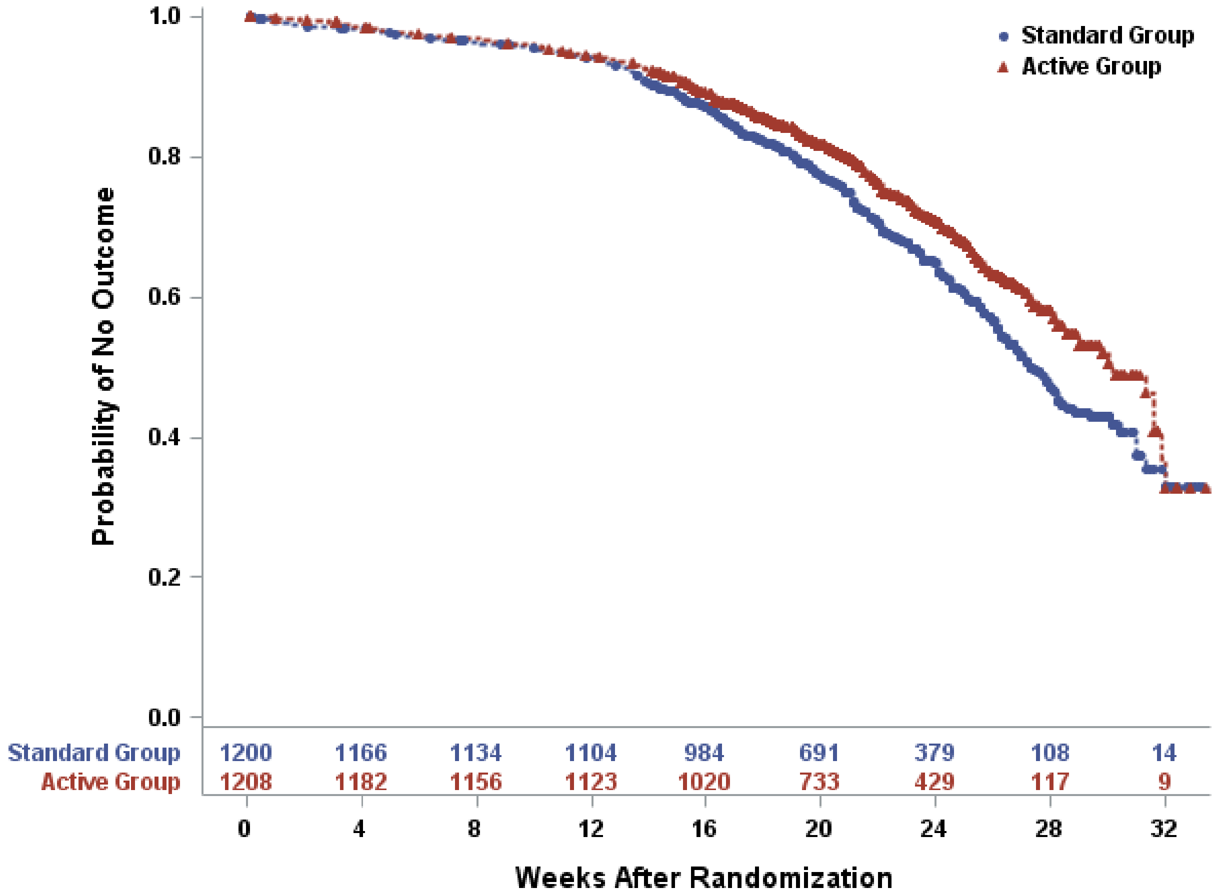
The last 2 columns report the rates of each antihypertensive medication at the last visit among those with at least 1 clinic visit form(n=2341).

Table S5. Serious adverse events as reported on HP15

	Active Treatment Group (N=1208)	Standard Treatment Group (N=1200)	
	Number of Events	Number of Events	Number of Events
Serious Adverse Event (Total)	155	178	333
Non-Death	113	126	239
Angioedema/anaphylaxis	0	1	1
Blood pressure related event (e.g., syncope, postural hypotension)	7	17	24
Congenital malformation discovered after randomization	26	19	45
Maternal acute renal failure	2	0	2
Maternal admission to ICU for any reason	8	19	27
Maternal cardiac arrest	1	0	1
Maternal cardiomyopathy	1	0	1
Maternal pulmonary thromboembolism	3	3	6
Maternal seizure	0	2	2
Maternal stroke/CVA	0	1	1
Pulmonary edema	6	7	13
Any Other Adverse Event	59	57	116
Maternal Death	1	2	3
Neonatal Death	5	8	13
Fetal Death (anytime post-randomization to delivery)	36	42	78
Adverse Event	646	573	1219

COVID-19 Cases	13	18	31

Figure S2. Survival Analysis: Kaplan-Meier Analysis for Time to Primary Outcome



Survival analysis for time to primary outcome indicates that patients randomized to the Standard Treatment group proceed to the primary outcome more frequently and at a higher rate than those randomized to Lower Blood Pressure Management (Active Treatment). Differences are statistically significant In a Cox proportional hazards model, we also see a significant effect benefit of treatment with hazard ratio (Active vs. Standard) 0.79 with 95% CI: 0.68-0.91.

Table S6. Primary Outcome Analysis with Results as Odds Ratios

	Imputation Analysis (n=2408)		Complete-Case Analysis (n=2325)			
Primary Outcome	aOR (95% CI)	P	Active treatment (n=1170)	Standard treatment (n=1155)	OR (95% CI)	p
Composite Outcome (any item below)	0.74 (0.62-0.88)	<0.001	353 (30.2%)	427 (37.0%)	0.74 (0.62-0.88)	<0.001
Preeclampsia with severe features	0.74 (0.61-0.89)		272 (23.2%)	336 (29.1%)	0.74 (0.61-0.89)	
Indicated preterm birth <35 weeks	0.68 (0.54-0.86)		143 (12.2%)	193 (16.7%)	0.69 (0.55-0.88)	
Placental abruption	0.92 (0.50-1.68)		20 (1.7%)	22 (1.9%)	0.90 (0.49-1.65)	
Fetal or neonatal death <28 days	0.81 (0.53-1.23)		41 (3.5%)	50 (4.3%)	0.80 (0.53-1.22)	
Safety Outcome (Alexander)	Imputation Analysis (n=2408)		Complete-Case Analysis (n=2283)			
Small for Gestational Age	aOR (95% CI)	P	Active treatment (n=1153)	Standard treatment (n=1130)	OR (95% CI)	p
<10th percentile	1.21 (0.95-1.54)	0.16	166 (14.4%)	138 (12.2%)	1.21 (0.95-1.54)	0.12
<5th percentile	0.86 (0.60-1.23)	0.44	59 (5.1%)	66 (5.8%)	0.87 (0.61-1.25)	0.45
Safety Outcome (Duryea)	Imputation Analysis (n=2408)		Complete-Case Analysis (n=2270)			
Small for Gestational Age	aOR (95% CI)	p	Active treatment (n=1146)	Standard treatment (n=1124)	OR (95% CI)	p
<10th percentile	1.05 (0.81-1.37)	0.71	128 (11.2%)	117 (10.4%)	1.08 (0.83-1.41)	0.56
<5th percentile	0.89 (0.61-1.29)	0.53	58 (5.1%)	62 (5.5%)	0.91 (0.63-1.32)	0.63

Missing values were estimated using characteristics within each treatment group that may be predictive of the composite outcome. The missing values were modeled within treatment group using baseline characteristics including diabetes status (yes/no), treatment status at enrollment (on BP meds vs. not on BP meds), age, BMI, and elevated BP at the first visit (SBP ≥ 150 and/or DBP ≥ 100). Multiple imputed data sets were developed with 5 replicates. The primary analysis was conducted on each of the imputed complete data sets and the final results were pooled.

The 95% confidence intervals are not adjusted for multiple comparisons.

Table S7. Per Protocol Analysis

	Imputation Analysis (n=2408)				Complete-Case Analysis (n=2281)				
Primary Outcome	aOR (95% CI)	p	aRR (95% CI)	P	Medications Group (n=1731)	Non-Medications Group (n=550)	OR (95% CI)	RR (95% CI)	p
Composite Outcome (any item below)	0.62 (0.51 - 0.76)	<0.0001	0.74 (0.65-0.83)	<0.0001	518 (29.9%)	224 (40.7%)	0.62 (0.51-0.76)	0.73 (0.65-0.83)	<0.0001
Preeclampsia with severe features	0.63 (0.51-0.77)		0.72 (0.62 - 0.83)		414 (23.9%)	184 (33.4%)	0.63 (0.51-0.77)	0.71 (0.62-0.83)	
Indicated preterm birth <35 weeks	0.53 (0.41-0.67)		0.58 (0.48-0.71)		212 (12.2%)	114 (20.7%)	0.53 (0.42-0.69)	0.59 (0.48-0.73)	
Placental abruption	0.60 (0.31-1.16)		0.60 (0.31-1.16)		25 (1.4%)	13 (2.4%)	0.61 (0.31-1.19)	0.61 (0.31-1.19)	
Fetal or neonatal death <28 days	0.87 (0.48-1.57)		0.87 (0.49-1.55)		44 (2.5%)	15 (2.7%)	0.93 (0.51-1.68)	0.93 (0.52-1.66)	

Each study participant in the CHAP study was evaluated for adherence to assigned treatment at randomization. For those randomized to Active Treatment, compliance with study medications was evaluated at each study visit. Those who were compliant for at least 80% of these visits were classified in the medications group for this analysis; otherwise they were classified in the non-medications group. For those randomized to Standard Treatment, compliance was evaluated at each study visit to determine if the participant was taking medications. Those correctly not taking medications for at least 80% of these visits were classified in the non-medications group for this analysis; otherwise they we classified in the medications group.

The 95% confidence intervals are not adjusted for multiple comparisons.

Table S8. Primary Outcome Sensitivity Analysis with Outcomes for 5 Patients Reclassified as Missing

	Imputation Analysis (n=2408)				Complete-Case Analysis (n=2320)				
Primary Outcome	aOR (95% CI)	P	aRR (95% CI)	P	Active treatment (n=1167)	Standard treatment (n=1153)	OR (95% CI)	RR (95% CI)	p
Composite Outcome (any item below)	0.74 (0.62-0.88)	0.0007	0.83 (0.74-0.92)	<0.001	353 (30.3%)	427 (37.0%)	0.74 (0.62-0.88)	0.82 (0.73-0.92)	<0.001
Preeclampsia with severe features	0.75 (0.62-0.90)		0.81 (0.70-0.93)		272 (23.3%)	336 (29.1%)	0.74 (0.61-0.89)	0.80 (0.70-0.92)	
Indicated preterm birth <35 weeks	0.70 (0.55-0.89)		0.75 (0.61-0.91)		143 (12.3%)	193 (16.7%)	0.69 (0.55-0.88)	0.73 (0.60-0.89)	
Placental abruption	0.94 (0.51-1.73)		0.93 (0.51-1.68)		20 (1.7%)	22 (1.9%)	0.90 (0.49-1.65)	0.90 (0.49-1.64)	
Fetal or neonatal death <28 days	0.82 (0.54-1.26)		0.84 (0.56-1.25)		41 (3.5%)	50 (4.3%)	0.80 (0.53-1.22)	0.81 (0.54-1.21)	

This sensitivity analysis considers that 5 study participants with possible outcomes were investigated and adjudicated as non-outcomes, but these did not include follow-up visit information. Thus something could have been reported after delivery that was not reflected in the available materials for review. We treat these 5 outcomes as missing in these analyses. Complete case results reflect n=2320. This table appears in the Supplementary materials for the primary manuscript.

The 95% confidence intervals are not adjusted for multiple comparisons.

The next sensitivity analysis considers an extreme scenario where all patients in the Lower BP group are assigned as having a primary outcome and all patients in the Standard BP group are assigned as not having a primary outcome. This scenario completely nullifies the beneficial effects observed above and indicates potential harm with higher rates of abruption and fetal/neonatal death in the Lower BP group. However, this is an extreme hypothetical example and is not supported by the results presented above.

Table S9. Extreme scenario 1, biasing away from benefit in Active BP arm

Outcome	Active BP (n=1208)	Standard BP (n=1200)	OR (95% CI)	RR (95% CI)	p
Composite Outcome (any item below)	391 (32.4%)	427 (35.6%)	0.87 (0.73-1.03)	0.91 (0.81-1.02)	0.10
Preeclampsia with severe features	310 (25.7%)	336 (28.0%)	0.89 (0.74-1.06)	0.92 (0.80-1.05)	
Indicated preterm birth <35 weeks	181 (15.0%)	193 (16.1%)	0.92 (0.74-1.15)	0.93 (0.77-1.13)	
Abruption	58 (4.8%)	22 (1.8%)	2.70 (1.61-4.44)	2.62 (1.61-4.25)	
Fetal or neonatal death <28 days	79 (6.5%)	50 (4.2%)	1.61 (1.12-2.32)	1.57 (1.11-2.22)	

The 95% confidence intervals are not adjusted for multiple comparisons.

The next sensitivity analysis considers another extreme scenario where all patients in the Lower BP group are assigned as not having a primary outcome and all patients in the Standard BP group are assigned as having a primary outcome. As expected, the significant effects observed in the primary analysis are amplified, and beneficial effects are observed for abruption and fetal/neonatal death.

Table S10. Extreme scenario 2, biasing toward benefit in Active BP arm

Outcome	Active BP (n=1208)	Standard BP (n=1200)	OR (95% CI)	RR (95% CI)	p
Composite Outcome (any item below)	353 (29.2%)	472 (39.3%)	0.64 (0.53-0.75)	0.74 (0.66 0.83)	<0.0001
Preeclampsia with severe features	272 (22.5%)	381 (31.8%)	0.62 (0.52-0.75)	0.71 (0.62-0.81)	
Indicated preterm birth <35 weeks	143 (11.8%)	238 (19.8%)	0.54 (0.43-0.68)	0.60 (0.49-0.72)	
Abruption	20 (1.7%)	67 (5.6%)	0.28 (0.17-0.47)	0.30 (0.18-0.49)	
Fetal or neonatal death <28 days	41 (3.4%)	95 (7.9%)	0.41 (0.28-0.59)	0.43 (0.30-0.61)	

The 95% confidence intervals are not adjusted for multiple comparisons.

Table S11. Population characteristics of pregnant women with chronic hypertension

Condition under investigation	Chronic hypertension
Special Conditions related to:	Pregnancy: The prevalence of chronic hypertension in the 2015-2018 US birth population was reported to be approximately 2%.
Age	Chronic hypertension increases with age. Median age category of women with chronic hypertension who gave birth in 2015-2018 was 30-34 years (vs. 25-29 years for the general birth population)
Race or ethnicity	Overall, chronic hypertension affects Black persons disproportionately in the United States. People with chronic hypertension who gave birth in 2015-2018 were 29.4% African American, 48.1% Caucasian, 15% Hispanic and 7.5% other ethnicity.
Overall representativeness of this trial	The age of participants enrolled in our study (mean 31-32 years) is representative of the general US birth population with chronic hypertension. Our study population had a higher proportion of Blacks (47.5%) and Hispanics (20.2%) than the general population of persons with chronic hypertension who gave birth (see above).

Grover S, Brandt JS, Reddy UM, Ananth CV. Chronic hypertension, perinatal mortality and the impact of preterm delivery: a population-based study. BJOG. 2022 Mar;129(4):572-579.

Table S12. Characteristics of all screened for CHAP

Characteristic	**Overall (n=29,772)**
Age at Screening, years*	31.7±5.8
Race/Ethnicity	
Black, non-Hispanic:	12468 (41.9%)
White, non-Hispanic:	9476 (31.8%)
Hispanic:	4411 (14.8%)
Other:	3417 (11.5%).

***5 missing**

Table S13. Mean AIC model fit statistic for multiple imputation

Outcome	Mean AIC – logistic	Mean AIC – log binomial
Composite	3028.4 ± 3.4	3028.7 ± 3.6
Preeclampsia with severe features	2746.9 ± 5.7	2746.9 ± 5.7
Indicated preterm birth <35 weeks	1961.8 ± 6.2	1963.1 ± 6.2
Placental abruption	442.9 ± 10.1	442.8 ± 10.1
Fetal or neonatal death <28 days	795.6 ± 8.2	793.8 ± 9.0
SGA<10th Percentile (Duryea)	1636.8 ± 14.1	1636.1 ± 13.9
SGA<10th Percentile (Alexander)	1859.3 ± 15.2	1859.2 ± 15.2

Values in the table above reflect the mean Akaike Information Criterion values for the multiple imputation analyses across 5 replicates. For each outcome, the log binomial model and the logistic regression models perform comparably.