A Pragmatic Multicenter Randomized Trial
Antihypertensive Therapy for Mild Chronic Hypertension during Pregnancy

CHRONIC HYPERTENSION AND PREGNANCY (CHAP)
PROJECT NIH/NHLBI Collaborative Project

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Clinical Protocol (v1.7)

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1. Introduction

1.1 Study Abstract

During pregnancy, chronic hypertension (CHTN) is the most common major medical disorder encountered, occurring in 2-6%. Often overlooked, the substantial negative effect of CHTN on pregnancy includes a consistent 3- to 5-fold increase in superimposed preeclampsia and adverse perinatal outcomes (fetal or neonatal death, preterm birth (PTB), small for gestational age (SGA) and placental abruption) and possibly a 5- to 10-fold increase in maternal cardiovascular and other complications (death, cerebrovascular accident, pulmonary edema and acute renal failure). Mild CHTN (BP <160/110) contributes to a large proportion of these adverse outcomes. While antihypertensive treatment of CHTN is standard for the general population (to reduce death and severe cardiovascular and renal complications), it is uncertain whether treatment during pregnancy reduces maternal or fetal complications, and there are concerns that decreased arterial pressure may reduce fetal blood flow and cause poor fetal growth or small-for-gestational-age (SGA) infants. Some authorities, including the American College of Obstetricians and Gynecologists (ACOG) and American Society of Hypertension (ASH) recommended against starting or continuing antihypertensive therapy for mild CHTN in pregnant women, particularly if BP is <160/105-110 mmHg. In a 2019 guideline, ACOG recommended against starting therapy for mild chronic hypertension and indicated that it is uncertain whether to continue or discontinue medications for those who present on therapy. The recommendation to withhold antihypertensive treatment in pregnancy conflicts with the broader public health goal to reduce BP in those with CHTN, but there is no evidence that withholding therapy during the brief period of pregnancy affects outcomes (despite a small increase in progression to severe hypertension). As a result, in practice, some providers prescribe antihypertensive therapy during pregnancy while others do not. For decades, authorities have consistently called for well-designed and powered trials to delineate the benefits and risks of pharmacologic therapy for mild CHTN during pregnancy.

Therefore, our multicenter consortium will conduct the Chronic Hypertension and Pregnancy (CHAP) Project, a large pragmatic randomized trial with a primary aim to evaluate the benefits and harms of pharmacologic treatment of mild CHTN in pregnancy. Pregnant women (N=2404) with mild CHTN (<160/105 mmHg) with or without prior antihypertensive treatment will be randomized to either primary therapy (mainly with labetalol or nifedipine ER) or to ACOG standard treatment (antihypertensive medication only if BP≥160/105 mmHg). The participants will be followed until delivery and for 6 (4-12) weeks postpartum (a separate long-term follow-up study is also planned). A formal interim analysis will be conducted after half of the expected total (n=1202) complete the study through the follow-up visit and all corresponding primary outcomes are adjudicated.

1.2 Primary Hypothesis

Antihypertensive therapy to *a BP goal* <140/90, compared with ACOG recommendations (no treatment), for mild CHTN reduces the frequency of key adverse maternal and newborn outcomes associated with CHTN including 1) a primary composite outcome **(Effectiveness)** including at least one of: i) fetal or neonatal death, ii) preeclampsia with severe features; iii) placental abruption, or iv) indicated PTB <35 weeks (i.e. not due to spontaneous preterm labor or membrane rupture and 2) SGA (birth weight <10th percentile) to assess **safety**.

1.3a Secondary Aims/Hypotheses related to the primary hypothesis include the following:

a) To better quantify the risks of severe maternal cardiovascular outcomes associated with mild CHTN during pregnancy and determine the impact of treatment.
b) To test whether antihypertensive (compared to withholding therapy) reduces the incidence of a composite of severe neonatal morbidities including at least one of bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH) grades III/IV.
c) To evaluate whether the effect of antihypertensive therapy for mild to moderate hypertension during pregnancy on primary outcome and SGA differs by a) prior antihypertensive therapy, b) racial-ethnic group, c) pre-existing diabetes, d) gestational age at randomization; e) maternal enrollment BMI .

1.3b Secondary Aims/Hypotheses un-related to the primary hypothesis include the following:

a) To assess whether antihypertensive treatment of mild CHTN during pregnancy (compared to standard care) increases post-pregnancy adherence to recommended therapy.
b) To assess the impact of postpartum treatment recommendations on maternal outcomes
c) To investigate the optimal gestational age to deliver women with CHTN in order to minimize maternal and perinatal complications. We will apply survival analysis methods to the trial population.
d) To collect and store biospecimens including maternal and cord blood for future biological and biophysical studies to understand the effects of antihypertensive therapy in pregnant women with mild CHTN.
e) To compare outcomes based on standardized pragmatic clinic BP vs. standardized automated clinic BP measures
f) To assess whether the effect of therapy on SGA differs by whether current national standard nomogram vs. individualized nomogram for birth weight is utilized.
g) To plan for a long-term follow-up study to evaluate the impact of treatment of mild-moderate chronic hypertension on long-term maternal and child outcomes.

1.4 Purpose of the Study Protocol

The purpose of this study is to evaluate whether a BP treatment strategy to achieve targets that are beneficial for non-pregnant adults (<140/90 mmHg) is safe and effective during pregnancy. This protocol describes the rationale, design and organization of the randomized clinical trial. It may be viewed as a written agreement among the study investigators. The protocol will be approved by the Consortium Steering Committee, and the designated Institutional Review Board (IRB) of each clinical center before recruitment begins. Any changes to the protocol during the study period will require the approval of the Steering Committee and the IRBs; major relevant changes will also require the approval of the Data Safety and Monitoring Board.

A manual of operations supplements this protocol with detailed procedures for implementation.

2. Background

2.1 Introduction

Chronic hypertension (CHTN) is preexisting hypertension or hypertension that occurs before 20 weeks of gestation (distinct from preeclampsia or gestational hypertension that occurs in the 2nd half of pregnancy). The importance of the proposed research to evaluate the effectiveness and safety of antihypertensive therapy for mild CHTN in pregnancy and the rationale and justification for the study are highlighted in the sections below.

2.2 CHTN as a major public health problem in the US and elsewhere:

The Centers for Disease Control and Prevention (CDC) estimates that almost 1 in 3 US adults (>68 million) have CHTN; this accounts for more than 350,000 deaths and $93 billion in health care costs annually.[1-3] Worldwide, deaths and costs are several fold greater.

2.3 Prevalence of CHTN during pregnancy:

CHTN complicates 2-6% (up to 260,000) of US births annually.[4-8] Historically, ≥4% of pregnant women enrolled in centers of the NICHD Maternal-Fetal Medicine Units (MFMU) Network (in which most of our proposing consortium centers participate) had CHTN.[5] CHTN affects 5-10% of reproductive age women and is more prevalent among African American, older and/or obese women.[1] Given temporal increases in obesity and older maternal age, the prevalence of CHTN in pregnancy is likely to rise. The diagnosis of CHTN (distinct from superimposed gestational hypertension or preeclampsia) and its classification into mild or severe disease in pregnancy are shown in Box 1.[8] The majority of pregnant women with CHTN have mild disease i.e. *BP<160/110*. For example, 640 of 763 women (83%) in the CHTN group of the NICHD MFMU trial of aspirin to prevent preeclampsia in high-risk women (HRA Trial, entry based on pragmatic clinic BP measurements)[9] had non-proteinuric CHTN with baseline BPs<155/100.

Box 1: ACOG Diagnosis/classification in pregnancy[8]

Diagnosis of CHTN:

- Use of antihypertensives before pregnancy
- Onset of hypertension before 20 weeks
- Persistence of hypertension after 12 weeks postpartum

ACOG Classification criteria:

- Mild: BP 140-159/90-109 mmHg
- Severe: BP≥160/110 mmHg

2.4 CHTN and Increased Adverse Obstetric Outcomes*:*

CHTN is associated with a 3- to 5-fold increase in several adverse pregnancy outcomes including superimposed preeclampsia. (See Table 1 for incidence and relative risks compared to those without CHTN):

Preeclampsia: Superimposed preeclampsia complicates 25-30% of pregnancies in women with CHTN and is a strong predictor of other adverse outcomes. The risk appears to be increased in those with a longer history of CHTN or with a prior history of preeclampsia.

Table 1: Adverse perinatal outcomes in CHTN patients

Outcome	Incidence %	RR (vs. no CHTN)*
Preeclampsia	25-30	3-4[6-7,10-12]
IUGR/SGA	11	2-3[7,13]
Abruption	1.5	2-3[4,6,7]
PTB <37 wk	38-50	3-4[5,8,10,12-13]
<35 wk	18-22	
Perinatal death	6-8	3-5[4,6-8]

**RR or OR relative to no CHTN based on referenced reports*

b) Perinatal morbidity: CHTN is associated with a marked increase in adverse outcomes (Table 1), including perinatal death, small for gestational age (SGA), placental abruption, and preterm birth (PTB).[4-13] As many as a third of women with CHTN have been reported to have poor fetal growth, and over 50% to have PTB.[8] The risk of adverse outcomes is particularly high among those who develop preeclampsia. Neonatal morbidity is also increased in offspring of women with CHTN, as reflected by a 24.3% incidence of NICU admission in the MFMU High Risk Aspirin trial.[11]The risk of cesarean delivery (increasing maternal morbidity in current and future pregnancies) is increased 2-fold. Preeclampsia is associated with a 2-3 fold increase in the risk of maternal death (particularly among African Americans) and is among the top 3 causes of maternal death in the US.[14-15] These significant risks are present in women with mild CHTN; the risks of preeclampsia and perinatal mortality among women with mild CHTN are at least 2-3 fold higher compared to women without CHTN.[4,10,16-18]

2.5 CHTN and Maternal Cardiovascular and other Medical Complications during Pregnancy*:*

Data from 2 recent retrospective studies also suggest that pregnant women with CHTN compared to those without CHTN may be at increased risk for death (0.1%) or maternal cardiovascular and other complications, including heart failure (0.2%), stroke (0.1-0.3%), need for ventilation (0.4%) and renal failure (0.2-0.6%) as well as myocardial infarction, hypertensive encephalopathy, and retinopathy.[19-20] Prolonged hospitalization (>6 days) occurred in 9.6%. The range of adjusted relative risks compared to pregnant women without CHTN was 3-5 for maternal death, 6-12 for pulmonary edema or heart failure, 5-8 for assisted ventilation, 4-7 for stroke, 10-16 for renal failure and 6-7 for prolonged maternal hospitalization (>6 days). These findings warrant confirmation in prospective studies.[19-20] Importantly, it is unknown whether these outcomes are influenced by treatment during pregnancy.

2.6 Treatment recommendations for CHTN

2.6.1 General child-bearing population*:* Pharmacologic treatment of CHTN is standard care for the nonpregnant population because of major long-term benefits, including reductions in death, myocardial infarction, heart failure, stroke and renal failure have been identified in randomized controlled trials.[21] Diagnosis, treatment and control of CHTN are key US public health goals.[22] Although BP thresholds for treatment and target BP goals may vary by age group, there is consensus that nonpregnant women of childbearing age should be treated if BPs are ≥140/90 to a goal <140/90.[23]

2.6.2 Pregnancy: ACOG and other authorities recommended that during pregnancy, antihypertensive treatment be withheld or discontinued for most women with CHTN (i.e. those with mild CHTN <160/105-110); for those with severe CHTN, the consensus is that treatment is prudent.[4,8,24-25] In its 2013 Task Force on Hypertension publication, ACOG recommended that treatment be withheld from women with BP<160/105 and that it is reasonable to discontinue antihypertensive treatment in early pregnancy if chronic hypertension is mild.[26] In a 2019 guideline, ACOG continues to recommend against starting therapy for mild chronic hypertension (<160/110), and for those on therapy, states it is uncertain whether to continue or not.[27] This conflicts with the recommendation for treatment of CHTN outside pregnancy. The ACOG recommendation results from the lack of data showing maternal or perinatal benefits of treatment during pregnancy and concerns about the safety of treatment for the mother and fetus. When oral treatment is undertaken in pregnancy, labetalol (bid or tid), nifedipine (daily) and methyldopa (bid or tid) are recommended as first line therapy; in 2019 ACOG suggested labetalol or nifedipine as first line.[26-27] While the physiologic changes associated with pregnancy may increase the clearance of these medications, there are no clinical trial data to support better efficacy for BP control and safety when more frequent dosing is utilized during pregnancy.

2.6.2.1 Lack of reliable data on the benefits of antihypertensive therapy during pregnancy*:* There are only a few small trials and limited data to guide management of CHTN in pregnancy, and the available data have not demonstrated significant maternal or perinatal benefit of treating mild CHTN.

1. **<u>Clinical trials</u>**:
   i. Sibai, et al randomized 300 women with mild CHTN <160/110 mmHg in the 1st trimester to methyldopa, labetalol, or no treatment.[16] Treatment lowered BP and reduced need to treat severe hypertension by 50% (from 11% to 6%) compared to no treatment. However, this did not translate to differences between groups in the risk of superimposed preeclampsia, abruption, PTB or SGA. The risk of preeclampsia

overall (18%) was high. Although the largest single treatment trial for CHTN in pregnancy, this study was underpowered to detect clinically important differences in outcomes between treatment groups.

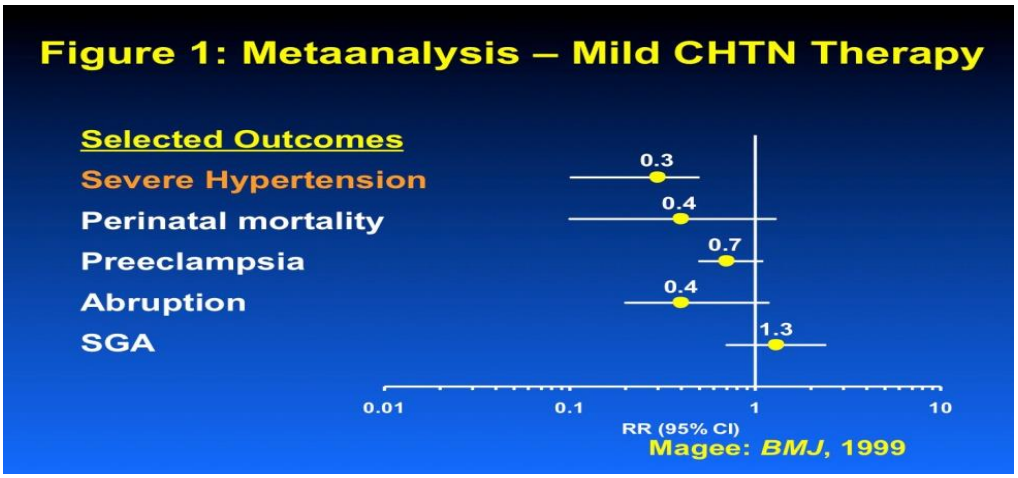
ii. The Italian Study Group randomized 283 women with CHTN or gestational hypertension (diastolic BP 90-109 mmHg) at 12-34 weeks (50% with CHTN) to nifedipine or no treatment.[28] Overall, the risks of PTB (55-63%), SGA (20-25%) and preeclampsia (15-23%) were high. Again, no between group differences were observed in SGA (RR 0.8; 95% CI 0.4-1.4), cesarean delivery (0.7; 0.4-1.1), or other outcomes such as preeclampsia or NICU admission. The study was underpowered for key outcomes, and results in those with CHTN were not provided.

iii. CHIPS trial:[29] The results of the Control of Hypertension in Pregnancy Study (CHIPS) Trial [clinicaltrials.gov #NCT01192412] were recently reported. Women with diastolic BP of 90-105 mm Hg (85-105 if already on antihypertensive medications) were randomized to either less-tight control (target diastolic BP, 100 mm Hg) or tight control (target diastolic BP, 85 mm Hg) at 14-33 weeks of gestation. Management decisions were based on pragmatic clinic BP measured three times, using the average of the 2nd and 3rd BP. Among 987 women, the primary outcome of pregnancy loss or high level-neonatal care for ≥48 hours did not differ between groups respectively (31.4% vs. 30.7 %). The frequency of severe hypertension was higher with less-tight control (40.6% vs. 27.5%). Other outcomes such as preeclampsia (48.9% vs. 45.7%), abruption (2.3% vs. 2.2%), or composite of "serious maternal complications" (3.7% vs 2.0% overall, mainly due to need for blood transfusion) did not differ between groups. The overall risk of SGA was not different between groups (16.1% vs. 19.7%). Of concern in the sub-group with CHTN, the risk of SGA was lower with less-tight control (13.9% vs. 19.7%; OR 0.66; 0.44-1.00) although underpowered. Of note, 56-59% of participants in the CHIPS trial were on antihypertensive therapy at randomization and a large majority received antihypertensive therapy by the end of the study. Study limitations among others include i) the lack of generalizability of the intervention strategy evaluated to the US setting where the national standard recommended by ACOG is not to treat mild chronic hypertension, ii) not applicable to many women presenting with chronic hypertension earlier in pregnancy than the 14-33 week enrollment window, iii) inadequate sample size to examine important pregnancy outcomes that are likely to be influenced by treatment (see data from systematic reviews below).[29] A statement from the Society for Maternal Fetal Medicine (SMFM) underscored the need to further evaluate antihypertensive therapy for mild chronic hypertension.[30]

2. **Systematic reviews**:

i. A single systematic review (7 trials in 623 women) focused solely on antihypertensive therapy in pregnant women with CHTN (excluding gestational hypertension or preeclampsia) at baseline.[31] The results are depicted in Figure 1. The observed reduction in severe hypertension in treated patients was not accompanied by significant reductions in key adverse pregnancy outcomes.[31] Results for indicated preterm birth, which is the specific type of preterm birth associated with CHTN, were not available.

ii. A Cochrane review included 4282 women with CHTN as well as gestational HTN or preeclampsia who were enrolled in 46 small trials of antihypertensive therapy.[32] Overall, antihypertensive treatment with any drug versus no treatment/placebo lowered the incidence of severe HTN (RR 0.5; 95% CI 0.41-0.61). There were no significant differences between treatment groups in preeclampsia (0.97; 0.83-1.13), eclampsia (0.34; 0.01-8.15), perinatal death (0.73; 0.50-1.08), PTB (0.98; 0.85-1.13), SGA (1.04; 0.84-1.27), abruption (1.83; 0.77-4.37) or maternal death. There were reductions in fetal loss (0.39; 0.17 - 0.93) and in neonatal respiratory distress syndrome (0.28; 0.12- 0.63) with treatment.



Methyldopa alone versus no treatment was associated with a lower incidence of fetal or neonatal death (0.35; 0.13 - 0.94). Analyses restricted to women with CHTN yielded similar results but corresponding data for fetal loss and respiratory distress were not available. Use of a placebo in the control group did not influence results. Considering the limited size and flaws of the individual trials (particularly combining patients with disparate types of hypertension), the authors concluded that:

i. it remains unclear whether anti-hypertensive therapy for mild CHTN in pregnancy is worthwhile; and
ii. larger trials are needed to provide reliable data on the benefits and harms of treatment for mild CHTN in pregnancy. Importantly, women with CHTN at baseline are distinctly different from those with gestational hypertension or preeclampsia, and perhaps more likely to benefit or suffer harm from therapy, and therefore should be studied separately.[32]

Careful examination of the above systematic review data reveals that several important outcomes are tilted in the direction of potential benefit. Combined with our preliminary data (below), this leads us to hypothesize that, with adequate power, antihypertensive therapy may be associated with perinatal benefits.

2.6.2.2 Concerns regarding the safety of antihypertensive therapy in pregnancy*:*

A meta-analysis of beta-blocker treatment for mild CHTN in pregnancy found an association with SGA (OR 2.46; 1.02-5.92).[33] Another meta-analysis suggested that decreasing BP with antihypertensives was associated with increased risk of SGA and lower birth weight.[34] Overall, the data associating beta-blocker therapy with SGA are not strong and are confined to atenolol. A secondary analysis of the CHIPS trial also suggested a significant

increase in SGA in the subgroup of pregnant women with chronic hypertension who were assigned to tight compared to less-tight management.[29,30] Since SGA is associated with perinatal mortality and newborn morbidities (including low Apgar score, hypoglycemia, respiratory distress and prolonged stay) as well as neurodevelopmental disability, evidence of maternal or fetal benefit is critical prior to recommending treatment of hypertension in pregnancy.[35] Specific growth parameters include birth weight and length, ponderal index, head and abdominal circumference and placental weight. Other potential effects include bradycardia, hypotension and hypoglycemia, although these are more likely due to the effects of CHTN (PTB and SGA) than antihypertensive therapy.[36-37] Data are lacking on the long-term impact on infants of CHTN and its therapy in pregnancy.

2.7 Rationale and Justification for a randomized trial

2.7.1 Longstanding calls for large clinical trials to evaluate the benefits and safety of antihypertensive therapy in pregnancy*:* For more than a decade, scientific bodies and professional organizations have persistently called for well-designed studies.

a) **Expert Reviews**: Expert reviews of antihypertensive therapy for mild CHTN in pregnancy consistently noted the lack of quality evidence to support antihypertensive therapy and the need for large randomized controlled trials to optimize management recommendations.[6-7,10,22,38-40] The NHLBI National High BP Education Program Pregnancy Working Group noted that higher risk of fetal loss in the 2nd trimester was observed among untreated women in early trials but not confirmed by later trials and that the few available trials in women with CHTN all appeared to have major flaws.[38]

b) **Professional Society Recommendations**: Professional organizations have provided inconsistent management guidelines for CHTN in pregnancy.[8,24-25,41] While ACOG and the American Society of Hypertension (ASH) recommend that treatment be withheld for women with mild CHTN, the Royal College of Obstetricians and Gynecologists (NICE Clinical Guidelines, UK) recommends treatment with "safe" medications consistent with the management of CHTN in adults in primary care.[8,41] The Society of Obstetricians and Gynecologists (Canada) recommends therapy to keep systolic BPs at 130-155 and diastolic BPs at 80-105 mmHg for uncomplicated CHTN.[24] These differences underscore the lack of high quality data to support a specific treatment approach. Importantly, all identify a need to study antihypertensive therapy in pregnancy. This need was highlighted by the SMFM in response to the CHIPS trial.[30]

The preceding underscores the public health significance and need for a well-designed trial to evaluate the benefits and harms of antihypertensive therapy for CHTN in pregnancy. Next, we address how information from such a trial will lead to innovations that will improve the care and outcomes of pregnancy.

2.7.2 INNOVATIONS

The study will answer critical questions about the impact of treating CHTN in pregnancy and lead to innovations in obstetric care worldwide. The assembled cohort of pregnant women with CHTN will create the opportunity for a follow-up study to further our knowledge of the long-term impact of CHTN in pregnancy.

a) **Pregnancy care**: By delineating the benefits and possible harms of antihypertensive therapy in pregnancy, the study will define the optimal management of CHTN in pregnancy. By using pragmatic clinic BPs and also collecting automated standardized BPs using an automated oscillometric device, we will be able to evaluate the benefits and harms of pragmatic vs. standardized automated BP. Furthermore, the optimal timing of delivery is controversial – some experts suggest no sooner than 39 weeks while others suggest 38 weeks or earlier.[42-43] Therefore, relating adverse maternal and perinatal outcomes to gestational age at delivery will help define the optimal window for delivery. The study will also quantify the risks of maternal death and cardiovascular complications in pregnant women with CHTN. Ultimately this knowledge will lead to improved health outcomes for pregnant women with CHTN and their infants. Our findings could impact as many as 260,000 women with CHTN (and their infants) annually in the US (given 4.3 million births[44]) and millions more worldwide.

b) **Post-pregnancy care**: If antihypertensive therapy of CHTN during pregnancy is shown to prevent adverse outcomes, a recommendation to treat all pregnant women with CHTN, regardless of severity, would resolve the conflict in treatment recommendations for pregnant women compared to the general hypertensive population. This may positively impact post-pregnancy treatment adherence, improve rates of BP control among reproductive age women, and reduce complications of CHTN in women (a Healthy People 2015 goal). By comparing treatment adherence in the postpartum period between randomized treatment groups, we will determine whether antihypertensive treatment during pregnancy influences postpartum treatment adherence. We will also document treatment status during any prior pregnancies at baseline and will conduct adjusted analyses to investigate how lack of antihypertensive treatment during recurrent pregnancies influences subsequent medication adherence.

c) **Other innovations**: The assembled trial cohort will provide the opportunity for future studies to address other uncertainties concerning the impact of CHTN in pregnancy. For example, little is known about: i) long-term effects of CHTN and its treatment on offspring; ii) biological mechanisms and mediators of the effects of CHTN in pregnancy. This project creates the opportunity for separately funded proposals to conduct studies on collected bio-specimens (e.g. bio-markers of adverse outcomes in pregnancy with CHTN) and follow-up of the cohort to define the long-term maternal and infant outcomes of CHTN and its treatment. These projects will be considered by various committees for their value and potential impact on the primary trial.

2.7.3 Supportive Preliminary data: Data from limited trials (reviewed above) and our study group's own preliminary studies support the hypothesis that antihypertensive therapy is potentially beneficial in pregnant women with mild CHTN.

a) **Preliminary data #1 – BP Control and pregnancy outcomes in women with CHTN[45]** : To test the hypothesis that in women with CHTN, mild HTN (BP 140-159/90-109) compared with controlled BP (<140/90) is associated with worse pregnancy outcomes, we carried out a secondary analysis of a cohort of women with CHTN (no diabetes, based on pragmatic clinic BP measurements) enrolled in the NICHD MFMU Network High Risk Aspirin Trial designed to evaluate aspirin use for preeclampsia prevention.[9] Outcomes were compared by baseline BP level on entry, analyzed both as a categorical (<140/90, 140-150/90-99, 151-159/100-109) and a continuous variable.

Results: 759 of 776 (97.8%) women were analyzed. BP differed significantly by race/ethnicity, smoking status, proteinuria, prior preeclampsia and antihypertensive use. The frequency of treatment initiated prior to pregnancy decreased while initiation during pregnancy increased with increasing BP. The incidence of adverse pregnancy outcomes (Table 2) increased with increasing BP for the composite outcome, perinatal death, indicated PTB and SGA. After multivariable logistic regression, outcomes remained higher among women with elevated baseline BP (Table 3). Similar models including both continuous systolic (S) and diastolic (D) BP revealed significant increases per 5mm Hg rise in DBP (but not SBP): primary composite (25% per 5mm Hg), perinatal death (31% per 5 mmHg), indicated PTB (26% per 5 mmHg) and SGA (22% per 5mm Hg).

We concluded that adverse pregnancy outcomes are more frequent with mild BP elevation (140-159/90-109) than with normal baseline BP, and increase with increasing BP. Therefore, antihypertensive therapy to control mild CHTN (particularly DBP) before or early in pregnancy might improve outcomes and clearly warrants further study, considering the limitations of this observational secondary analysis. The increase in adverse outcomes associated with the lower range of mild CHTN (140-150/90-99) is noteworthy.[45]

Table 2: Incidence of adverse pregnancy outcomes by BP category (mm Hg)

	<140/90 (n = 478)	**140-150/90-99 (n = 221)**	**151-159/100-109 (n = 60)**	**P-value (trend)**
Composite Outcome (%)	11.7	22.6	30.0	**<0.0001**
Perinatal Death (%)	3.1	7.2	10.0	**0.0026**
Severe PreE (%)	1.9	5.9	1.7	**0.1335**
Abruption (%)	1.5	1.4	1.7	>0.999
Indicated PTB <35 (%)	7.7	16.3	26.7	**<0.0001**
Miscarriage < 20 weeks (%)	0.8	0.9	0	0.7673
SGA <10 percentile	8.8	12.3	23.7	**0.0012**

Table 3: Adjusted OR (95% CI) for selected pregnancy outcomes by BP*

	<140/90	**140-150/90-99**	**151-159/100-109**
Composite Outcome (%)	1 (Ref)	**2.3 (1.5-3.6)**	**2.9 (1.5-5.8)r4**
Perinatal Death	1 (Ref)	**2.6 (1.2-5.7)**	**2.9 (0.9-9.1)**
Indicated PTB<35	1 (Ref)	**2.2 (1.3-3.7)**	**3.5 (1.7-7.3)**
SGA <10%	1 (Ref)	**1.6 (0.9-2.8)**	**3.8 (1.8-7.9)**

*Adjusted for age, nulliparous, race, BMI, gestational age at randomization, smoking, proteinuria, HTN meds prior to pregnancy, HTN meds started during pregnancy, ASA group

b) **Preliminary data #2 - University of Alabama at Birmingham (UAB) Data**: A query of the UAB perinatal database from 2000-2011 revealed findings consistent with the reviewed literature. The prevalence of CHTN was 4%. Adverse outcomes were significantly higher in those with CHTN (vs. those without): preeclampsia – a 24% (vs. 5.5%), perinatal death – 5% (vs. 1.7%) and SGA – 11% (vs. 6%).

c) **Preliminary data #3 - Survey of Academic Centers**: We surveyed providers at 21 centers affiliated with the NICHD MFMU Network (including consortium centers) in 2011 about current policy concerning antihypertensive therapy in pregnancy. Equipoise and dearth of information concerning treatment in pregnancy were reflected in the wide practice variations (Table 4). The majority of providers indicated that they will be willing to not start treatment (90%) or to discontinue treatment (85%) in the setting of a clinical trial to determine the optimal mode of practice regarding antihypertensive therapy during pregnancy.

Table 4: Results of survey about management of CHTN at US academic sites in 2011 (N=21)

Management issue during pregnancy	Options/Prevalence (%)		
	Yes	**No**	**Varies**
Start medication for new mild CHTN	42%	42%	16%
Stop treatment for known mild CHTN	27%	68%	5%
	Labetalol	**Aldomet**	**Nifedipine/CCB**
First line therapy	68%	21%	11%
Second line therapy	33%	17%	50%
Treatment absolutely indicated	**Systolic>160**	**Diastolic>100**	
	63%	68%	

Although ACOG recommended no treatment if CHTN is mild, centers were divided concerning current practice. However, the ACOG Practice Bulletin on chronic hypertension of 2012 further reaffirmed the recommendations to not start treatment or to discontinue it if hypertension is mild; consistent with the ACOG guidelines, the majority of centers used labetalol as first line therapy.[8]

In summary, regardless of findings, the trial will change practice by providing critical evidence to inform treatment recommendations for this common co-morbid condition in pregnancy. Since the at-risk population is growing, the impact will increase over time, and benefits will apply to millions of women of reproductive age.[44,46]

3. Study Design

CHAP is a large pragmatic trial with adaptive sample size focusing on women who will be enrolled early in pregnancy with preexisting or newly diagnosed mild CHTN. The pragmatic approach follows the seminal design of the Hypertension Detection and Follow-up Program which compared stepped care to referred care, because of the cost, ethics and complications of a placebo controlled trial.[47]A pragmatic open label design has been used successfully in studies of antihypertensive therapy.[48-50]

3.1 Primary Research Question

Does antihypertensive therapy to a pragmatic clinic BP goal <140/90, compared with ACOG recommendations (no treatment), for mild CHTN reduce the frequency of key adverse maternal and perinatal outcomes associated with CHTN including 1) a primary composite outcome **(Effectiveness**) including at least one of: i) fetal or neonatal death, ii) preeclampsia with severe features; iii) placental abruption, or iv) indicated PTB <35 weeks (i.e. not due to spontaneous preterm labor or membrane rupture, and 2) SGA (birth weight <10th percentile), to assess **safety**.

3.2a Secondary Research Aims Related to Primary Question:

a) To better quantify the risks of severe maternal cardiovascular outcomes associated with mild CHTN during pregnancy and determine the impact of treatment.
b) To test whether antihypertensive (compared to withholding therapy) reduces the incidence of a composite of severe neonatal morbidities including at least one of BPD, ROP, NEC, IVH grades III/IV
c) To evaluate whether the effects of antihypertensive therapy for mild to moderate hypertension during pregnancy on the primary outcome and SGA differ by a) prior antihypertensive therapy, b) racial-ethnic group, c) pre-existing diabetes, d) gestational age at randomization; e) maternal first pregnancy BMI.

3.2b Secondary Research Aims Unrelated to Primary Question:

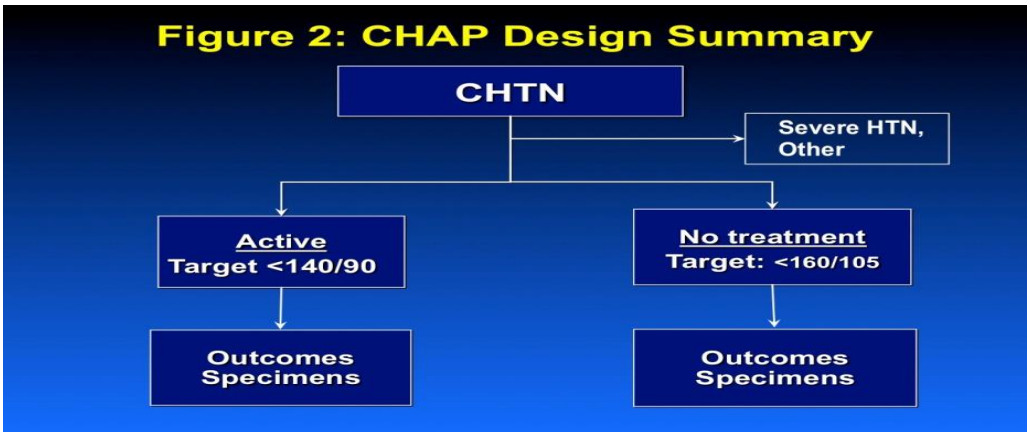
d) To assess whether antihypertensive treatment of mild CHTN during pregnancy (compared to withholding therapy) influences post-pregnancy adherence to recommended therapy.
e) To assess the impact of postpartum treatment recommendations on maternal outcomes
f) To investigate the optimal gestational age to deliver women with CHTN in order to minimize maternal and perinatal complications. We will apply survival analysis methods to the trial population.
g) To collect and store biospecimens including maternal and cord blood for future biological and biophysical studies to understand the effects of antihypertensive therapy in pregnant women with mild CHTN.
h) To compare outcomes by standardized pragmatic clinic BP vs. standardized automated clinic BP measures.

i) To assess whether the effect of therapy on SGA differs by whether current national standard nomogram vs. individualized nomogram for birth weight is utilized.

j) To plan for a long-term follow-up study to evaluate the impact of treatment of mild-moderate chronic hypertension on long-term maternal and child outcomes

3.3 Design Summary

This study is a multicenter randomized controlled clinical trial of 2404 women with randomization stratified by center (Figure 2). Patients with mild CHTN (based on pragmatic clinic BP measurements <160/105) will be randomized to either treatment with a first-line antihypertensive agent recommended by ACOG (labetalol or nifedipine ER supplied by the study) or other provider preferred medication (not supplied by the study), or no anti-hypertensive treatment. Consistent with the pragmatic design to evaluate the policy of therapy and not a specific medication, rarely, women who have a strong preference for their own established medication (e.g. intolerance of other medications) will be included in the study (and will use their own supply).



For participants in the active treatment group, labetalol dose, nifedipine ER dose or other antihypertensive medication dose will be escalated as needed to achieve target BP (<140/90). Dosing frequency may be increased to tid in order to control BP or to reduce side-effects. If the maximum tolerated oral dose of the first line agent is reached and BP is not at target, 2nd line treatment (labetalol or nifedipine ER) will be initiated to achieve the target BP. After delivery, goal BP will be <140/90 for at least two weeks.

In the comparison group, treatment will not be started if BP remains <160/105; for BP ≥160/105, treatment with a first line agent (labetalol or nifedipine ER) will be initiated and maintained at the lowest dose needed to keep BP <160/105. Goal BP after delivery will follow usual practice at each site.

Analysis will be by intent to treat.

3.4 Population and Eligibility Criteria

a) Setting: This multicenter study will be conducted at 16 or more academic Ob/Gyn centers at sites located across the US, most with a high prevalence of CHTN.

b) Inclusion criteria:

i. Women with either a new or a known diagnosis of CHTN during pregnancy receiving prenatal care at participating centers will be eligible for screening:

First, a diagnosis of CHTN will be verified as follows:

- New CHTN: This requires elevated SBP ≥140 and/or DBP≥ 90 mm Hg on two occasions at least four hours apart prior to 20 weeks' gestation or before pregnancy in a patient who has never received antihypertensive therapy for a diagnosis of CHTN. The BPs on the day of screening may count towards confirming the diagnosis as well as towards entry BP criteria.
- Known CHTN: Documented prior or current use of antihypertensive therapy for BP control confirms the diagnosis of known CHTN during pregnancy. By definition, these patients do not require confirmation of an elevated BP to meet diagnostic criteria.

Next, entry BP thresholds based on the pragmatic clinic BP depend on whether the patient is currently on antihypertensive therapy and adherent:

- If untreated or not adherent with monotherapy (i.e. has not taken medication within 24 hours of randomization): Pragmatic clinic BP at randomization must be within the range of 140-159 systolic or 90-104 diastolic. The pragmatic clinic BP will be 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) are excluded – consistent with both current ACOG guidelines and our preliminary survey findings (more providers may treat patients at these upper BP ranges).[8] Excluding the upper range of mild CHTN provides a buffer to protect protocol adherence and inclusion of more severe chronic hypertension.*
- If known CHTN and adherent with monotherapy within the previous 24 hours (including combination agents in a single tablet): Standardized BP at randomization must be SBP <160 and DBP<105(including those with BP<140/90). This is consistent with standard ACOG definitions of CHTN in pregnancy and management recommendations.

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

- BPs used for entry into the study and management will be based on pragmatic clinic BP measurements. Clinical personnel at all sites will be in-serviced on the pragmatic BP measurement protocol.

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

iii. Viable pregnancy <$23^{0/7}$ weeks of gestation (without preeclampsia / or gestational hypertension). For those with a history of chronic hypertension being randomized between 20-$22^{6/7}$ weeks gestation, documentation of urine protein <+1 on dipstick OR <0.3 on protein/creatinine ratio OR <300 mg/24 hours on the date of randomization is required to rule out preeclampsia. In women who have no history of chronic hypertension, at least 2 blood pressures ≥140/90 prior to 20 weeks must be documented to distinguish from gestational hypertension. ***Gestational age determination:*** *ACOG criteria (most recent) with ultrasound required prior to randomization.*[51]

c) Exclusion criteria

i. Pragmatic 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.

** Of note, BP elevations due to antepartum or postpartum preeclampsia or gestational hypertension in a *prior* pregnancy or 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 (see manual of procedures)

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 will not be enrolled in other trials without prior approval by protocol committee)
xiv. Physician or provider refusal
xv. Patient refusal

3.5 Gestational Age Determination

Gestational age will be determined based on the best estimate used by providers after taking into consideration the date of the last menstrual period (LMP) and findings of the first ultrasound as recommended by ACOG.[51] The American College of Obstetricians and Gynecologists, the American Institute of Ultrasound in Medicine, and the Society for Maternal-Fetal Medicine make the following recommendations regarding the method for estimating gestational age and due date:

- If no ultrasound examination has been performed previously, one will be performed before the patient is randomized.
- The first day of the last menstrual period (LMP) is determined. Using the LMP date, the gestational age at the time the initial US is performed will be determined.
- Ultrasound measurement of the embryo or fetus in the first trimester (up to and including 13 6/7 weeks of gestation) is the most accurate method to establish or confirm gestational age. Measurements of various parameters and their correlating gestational ages will be obtained from the first ultrasound examination obtained by the standard ultrasound method at each institution
- If pregnancy resulted from assisted reproductive technology (ART), the ART-derived gestational age should be used to assign the estimated due date (EDD). For instance, the EDD for a pregnancy resulting from in vitro fertilization should be established using the age of the embryo and the date of transfer.
- When determined from the methods outlined in this document for estimating the due date, gestational age at delivery represents the best obstetric estimate for the purpose of clinical care and should be recorded on the birth certificate. For the purposes of research and surveillance, the best obstetric estimate, rather than estimates based on the LMP alone, should be used as the measure for gestational age.

Table 2. Guidelines for Redating Based on Ultrasonography

Gestational age at first ultrasound by LMP	Ultrasound agreement with LMP
up to 8 6/7 weeks (by CRL)	≤5 days
9 0/7 weeks to 13 6/7 weeks (by CRL)	≤7 days
14 0/7 to 15 6/7 weeks	≤7 days
16 0/7 to 21 6/7 weeks	≤10 days

CRL = Crown Rump Length

3.6 Study Groups

Randomization will be stratified by center, and there will be 2 intervention groups:

Group 1 (active treatment): 1st line antihypertensive therapy (labetalol or nifedipine ER supplied by the study) or other preferred medication (not supplied by the study) is started at the time of randomization. Treatment will be escalated to the maximum tolerated dose of a single agent prior to initiation of the preferred 2nd line medication (nifedipine ER or labetalol) to achieve target BP: <140/90.

Group 2 (standard comparison): This group will not receive antihypertensive therapy unless BP is ≥160 systolic or ≥105 diastolic (allowing a 5mmHg treatment buffer). If on antihypertensive therapy at the time of randomization, the antihypertensive therapy will be stopped at randomization. If pragmatic blood pressures reach ≥160 systolic or ≥105 diastolic, the lowest dose of labetalol or nifedipine ER needed to keep BP below this threshold will be started. (Based on available trials and systematic reviews, we estimate that 10% of women in this group will require BP treatment.)[16, 32] **As part of routine clinical practice, providers will ask patients on medication about adherence before titrating the medication dose. In addition, research staff will monitor patient adherence through pill counts at the time of drug refills. Of note, if patients/providers prefer to use a medication other than nifedipine or labetalol according to protocol after randomization, methyldopa or other appropriate antihypertensive may be used (however, this will not be provided by the study) and the patients will remain in the trial for the intent-to-treat analyses.**

3.7 Informed Consent

Written informed consent must be obtained before entry into the randomized trial. Full disclosure of the nature and potential risks of participating in the trial including the risks of being in the standard care group will be made. Each center will develop its own consent form according to the requirements of its own institutional review board using the template consent form in Appendix 1. Each center will also develop its own patient research authorization documents, as required by the HIPAA Privacy Rule, following the guidelines of its own institution, but adhere to a minimum standard for the study. A copy of the signed consent form will be provided to the patient. SMART IRB central IRB review process will be used in an attempt to streamline IRB review for those centers that are registered with SMART IRB.

Women who are not fluent in English will be enrolled by persons fluent in their language. Both verbal and written informed consent and authorization will be obtained in that language; if this is not possible the patient will be excluded.

4 Study Procedures

4.1 Training and certification of Staff and Centers

Training of staff and pilot testing of procedures are crucial to standardized study procedures including BP measurement, quality control and data quality. Two different training models will be used: central training for study staff and the train-the-trainer approach. In the central training aspects of the CHAP training effort, all relevant staff members from all clinical sites will be convened in a centrally administered training session. This approach is cost- efficient and contributes to uniformity of the training experience and thereby to uniformity of data quality across sites. Refresher training sessions will occur yearly or as needed.

In the train-the-trainer aspect of the training effort, the research staff at each clinical center will provide training sessions as well as video training for clinical staff at their sites that are charged with measuring participants' BP and following the treatment algorithms of the study protocol. Clinical center staff will also provide training sessions in addition to video training to persons unable to attend the central training session and to newly hired staff as turnover occurs. In addition, they will organize 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 initiation to enroll and randomize participants is dependent upon completion of a series of preliminary tasks. Sites must submit an implementation plan that will be reviewed and approved by the coordinating center. Appropriate regulatory approvals (IRBs), and letters of agreement must be in place. Site staff training and certification must be done, and receipt of all study supplies (including medications, Omron devices and biospecimen labels) confirmed by the site. The clinical center will provide the appropriate assistance to their clinical sites toward these ends. This may include site visits by the DCC and/or CCC if necessary, to ensure that the study enrollment and randomization process follows proper study procedures. A training manual and video instruction supplement this section.

4.2 Screening for eligibility and consent

If feasible, patients will be screened and followed-up in a dedicated hypertension clinic. Data obtained from the screening by the standard ultrasound method at each institution and randomization visits must be supported in the patient's source documentation. Visit data will be entered into the CHAP database within a specified time frame determined by the DCC, which varies by form (i.e. SAEs, routine visits, etc.).

The participant's inclusion and exclusion criteria will be verified as will her interest in the study. The informed consent process will be conducted by trained research staff and will include all aspects of the study and a full disclosure of the risks, benefits, procedures, and alternatives. The study consent and HIPAA authorization will be signed after all questions have been discussed and answered. Collection of baseline information, including such items as contact information, BP measurements, demographic and pregnancy history information,

concomitant medications, and lifestyle information will follow the informed consent process. Automated devices will be used at baseline for standardized BP measurement and comparison.

4.2.1 Pragmatic Clinic BP Measurement and Quality Control

The clinical staff at each site will be in-serviced on the following aspects of blood pressure measurement using the usual clinic BP device and standard procedure outlined 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) If the initial blood pressure is <140/90, that blood pressure may be used for clinical decision making / enrollment
5) If the initial blood pressure is ≥140/90, the blood pressure should be repeated. The second (repeat) blood pressure should then be used for clinical decision making / enrollment.

4.2.2. Standardized Automated BP Measurement

Once a patient is consented and randomized, BP measurements will be taken by a study trained and certified examiner using the study OMRON automated device.[52-60] Attention will be paid to use of the appropriate patient position (sitting), period of rest, consistent arm (right), sized cuff and repeated measurements. A detailed procedure is provided in the manual.

Quality control: Special attention must be placed on assessment and maintenance of the instrument's accuracy as per the manual that accompanies the instrument.

4.3 Randomization and baseline visit procedures

Randomization may occur upon confirmation that all inclusion/exclusion criteria are satisfied and after verification of participant consent and HIPAA authorization. Of particular importance, careful consideration will be given the patient's prior history of CHTN, current use of and adherence to antihypertensive therapy, and standardized clinic BP measurement to determine eligibility and the appropriate study algorithm to follow (see below). Study staff will also verify participant contact information and obtain a Release of Information, as permitted by local policy, to collect outcome and serious adverse event (SAE) documentation. Patients will be assigned to treatment groups with a concealed randomization allocation sequence using a web-based application managed by the Data Coordinating Center (DCC). Randomization will be stratified by clinical center to assure balance between treatment groups with respect to anticipated differences in the center population and possible differences in patient management. There will be 2 categories of patients with new or known mild chronic hypertension randomized:

a) Women with untreated CTHN: This group includes women with a new diagnosis of CHTN as well as women with a prior diagnosis of CHTN but not being treated. All of these patients must have pragmatic

clinic BP 140-159/90-104 to be eligible for randomization. (**Note that criteria for a new diagnosis of chronic hypertension includes elevated BPs on at least 2 occasions a minimum 4 hours apart; a diagnosis of known chronic hypertension is based on current or prior antihypertensive therapy for a diagnosis of chronic hypertension).

b) Those on a single antihypertensive agent who are adherent with their meds:
    - Adherent with medications defined as having taken medication within the last 24 hours of randomization.
    - BP inclusion range will be standardized pragmatic SBP ≤159 and DBP ≤104 for a woman in this group (including those with BP<140/90).

The enrollment BPs will be based on the single blood pressure <140/90 or the repeat blood pressure measurement (if ≥140/90) for clinical decision making (pragmatic clinic BP).
If a pragmatic clinic BP is not available for any reason, the automated/OMRON BP may be used to determine entry.
Once the participant is randomized, the treatment algorithms will be conspicuously placed in her medical record (whether electronic or paper medical record is utilized) such that providers will be aware of treatment plan at all times. The randomly assigned treatment plan will be reviewed with the participant. If a patient is randomized to active treatment, labetalol, nifedipine ER (supplied by the study) or other provider preferred medication (not supplied by the study) to maintain blood pressure <140/90 will be prescribed on the day of randomization. If a patient is randomized to no treatment, any antihypertensive therapy will be stopped on the day of randomization. In both groups, BP measurement will follow recommended guidelines for pregnancy including attention to appropriately sized cuff, period of rest, patient position and repeated measurement to confirm elevation. Baseline data consisting of the pragmatic clinic BP measurements at enrollment, the standardized Omron BP measurements, urine protein results, body mass index, and other prenatal data including baseline BP (first documented BP within 3 months prior to or during pregnancy) will be collected at the randomization visit.

Maternal whole blood, plasma, serum and paxgene specimens will be collected at the randomization and midtrimester (24-30 weeks gestation) visits and stored for future research. Specific collection tubes that will allow for genetic testing and RNA preservation (paxgene) will be used. After delivery, maternal whole blood, plasma and serum will be collected. Cord blood for whole blood, plasma and serum will also be collected at delivery. The placenta will be sent to hospital pathology lab for routine pathology sampling and analysis.

In the active treatment group, a month's supply of the prescribed (supplied) first line medication will be provided to the patient. The medication dose and/or frequency of dosing will be escalated as necessary during subsequent prenatal visits following the specific study treatment algorithm. If the maximum dose of the first

line agent is reached and BP is still uncontrolled, 2nd line therapy (labetalol or nifedipine ER) will be prescribed as indicated to attain BP<140/90. After delivery, study medications or other appropriate BP medication at the provider's discretion will be used to target the goal BP < 140/90 for at least two weeks postpartum.

In the standard comparison group, participants are randomized to no antihypertensive treatment. They will receive education on the treatment algorithm for the no medication group and will follow the routine obstetric management in place at the clinical site unless the BP increases to a range ≥160/105. A first line agent will be provided to the participants in the comparison group whose BP reaches ≥ 160/105 at the minimum starting dose and only escalated as indicated to keep the BP below 160/105. Dosage frequency may be increased (to tid for labetalol or bid for nifedipine ER) if necessary. After delivery the goal BP for treatment will be according to usual care standards at the site.

4.3.1. Medication dosing: Active Treatment arm

Either first line medication (labetalol or nifedipine ER) may be initiated based on the patient's medical history, patient's past experience with antihypertensive medications, and provider preference/expertise. The starting dose and escalation of therapy, supplied by the study, in the active treatment arm are as follows

Labetalol:

- Will be started at 200 mg bid OR at the patient's current dose if currently on labetalol
- Labetalol will be escalated in increments of 200 mg bid to achieve blood pressures <140/90
- Labetalol dose may be divided into tid dosing for symptoms suggesting intolerance (headaches, fatigue, hypotension with high doses etc.)
- The maximum dose of labetalol is 2400 mg/day (1200 mg bid or 800 mg tid)
- If the maximum tolerated dose of labetalol is reached, nifedipine ER may be started. If nifedipine ER is contraindicated, or the patient is already on a maximum dose of nifedipine ER, a third line agent such as methyldopa may be initiated (although not supplied by study).

Nifedipine ER:

- Will be started at 30 mg Qday or at the patient's current dose if currently on nifedipine ER
- As this is an ER formulation, the pill should not be divided
- Nifedipine ER will be escalated in increments of 30 mg Qday to achieve blood pressures <140/90
- Nifedipine dose may be divided into bid dosing for symptoms, hypotension with high doses, or hypertension between doses
- The maximum dose of nifedipine ER is 120 mg/day
- If the maximum dose of nifedipine ER is reached, labetalol may be started. If labetalol is contraindicated, or the patient is already on a maximum dose of labetalol, a third line agent such as methyldopa may be initiated (although not supplied).

4.3.2. Medication Dosing: Standard Care per ACOG (No Treatment) arm

Blood pressure medication will be initiated for clinic BPs averaging ≥160/105. Either first line medication (labetalol or nifedipine ER supplied by the study) or provider preferred medication (not supplied by the study) may be 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 is <160/105.

Labetalol:

- Labetalol will be started at 100-200 mg bid.
- Labetalol will be escalated in increments of 100-200 mg bid to achieve blood pressures <160/105
- Labetalol dose may be divided into tid dosing for symptoms of fatigue, hypotension with high doses or hypertension between doses
- The maximum dose of labetalol is 2400 mg/day (1200 mg bid or 800 mg tid)
- If the maximum tolerated dose of labetalol is reached, nifedipine ER may be started. If nifedipine ER is contraindicated, or the patient is already on a maximum tolerated dose of nifedipine ER, a third line agent such as methyldopa may be initiated (not supplied).

Nifedipine ER:

- Will be started at 30 mg Qday
- As this is an ER formulation, the pill should not be divided
- Nifedipine ER will be escalated in increments of 30 mg Qday to achieve blood pressures <160/105
- Nifedipine ER dose may be divided into bid dosing for symptoms, hypotension with high doses, or hypertension between doses
- The maximum dose of nifedipine ER is 120 mg/day
- If the maximum tolerated dose of nifedipine ER is reached, labetalol may be started. If labetalol is contraindicated, or the patient is already on a maximum dose of labetalol, a third line agent such as methyldopa may be initiated (but is not supplied by the study).

4.4 Participant Management

4.4.1 Clinical management

A limited predefined management protocol will enhance the success of this pragmatic trial:

- A summary of the research management algorithm for patients in each of the two study groups will be strategically posted at clinic locations and will be placed in each participant's medical record; trained clinical (or research) staff will be available to measure pragmatic clinic BP at each visit.
- Routine pregnancy care at each center will be given to patients by clinical providers trained in the study protocol.

- Prescribed antihypertensive therapy according to study protocol will be supplied by the research team or designated pharmacist at each center/site until at least the time of delivery. After delivery the study medication or another appropriate antihypertensive agent will be used for at least 2 weeks after delivery.
- Prenatal visits will generally occur per local clinical standards at each site: every 1-3 weeks until 32-34 weeks gestation when weekly or more frequent visits will be indicated (depending on antenatal testing initiation policy) at the discretion of the provider.
- After 20 weeks, standard clinical care suggests that preeclampsia should be excluded by a clinical diagnostic work-up (including urine protein, serum creatinine, CBC and liver enzymes as necessary) and adherence to therapy considered before enrolling patients or escalating dose due to elevated BP.
- Patients will receive lifestyle modification counseling per the routine clinical practice at each center for any patient with hypertension (nutrition counseling, exercise/physical activity advice and smoking and/or alcohol cessation interventions).
- Ultrasound for anatomy or fluid/growth and antenatal testing will be per clinical center's routine.
- Timing of delivery preferably no earlier than 38-39 completed weeks unless indicated earlier for obstetric or medical reasons according to local guidelines (consistent with ACOG recommendations)

4.4.2 Research management: Study personnel will monitor each participant at each clinic visit (in person or remotely) to review the treatment plan based on the pragmatic clinic BP. This pragmatic clinic BP will be based on the usual clinic BP (single BP <140/90 or repeat BP measurement if ≥140/90. If the pragmatic clinic BP is elevated above the threshold that warrants treatment adjustment (≧140/90 for active arm and ≧160/105 for standard comparison group), the provider will take medication adherence into consideration to determine if any changes in study medications or doses are indicated. Study personnel will dispense additional medication as needed per study protocol. At scheduled clinic visits, participants will be asked about adherence to the medication regimen and off-study BP medications. If the participant's response to this question indicates a possible problem with adherence, and the participant is not at the appropriate BP target, this will be taken into consideration in dose adjustments.

Either clinic or study personnel will measure seated BP and heart rate at each clinic visit after a rest period using the routine clinical procedures.

Management of patients intolerant of treatment regimen

- For adverse effects such as hypotension (maternal BP<90/60) and persistent dizziness, headaches, lightheadedness or fatigue and no other potential cause other than the medication, dividing the current dose into more frequent doses will be used (e.g. tid instead of bid for labetalol and bid instead of daily for nifedipine ER) consistent with FDA recommendations. If this does not help the next step will be to reduce the daily dose of the medication to keep the BP ≥ 90/60 before switching to an alternative medication.

- For major reactions such as an allergic reaction to the first line medication, it will be discontinued and replaced with the alternate first line medication. If both labetalol and nifedipine are contraindicated, other acceptable medications such as methyldopa will be prescribed at the discretion of the clinical provider. The patient will still be followed by the study in an intent-to-treat fashion.

Adherence to antihypertensive medications will be assessed as follows:

a) The clinical provider (with the help of study staff as applicable) will assess adherence according to usual clinical routine to determine whether the participant has been adherent within the past 24 hours. For example, the provider could ask "When was the last time you took your medication? "Do you take your medication every day?" The provider will use this information to determine whether to titrate the BP medication dose(s) as clinically indicated.

b) At clinic visits when the patient requires a medication refill, study staff will conduct a pill count of the patient's study medication and record it. This will be used to estimate adherence. Given the pragmatic nature of the study, a more elaborate plan to monitor adherence will not be implemented by the research team.

All participants will be probed about off-study use of antihypertensive medication(s), alternative medications, and other vasoactive drugs during the clinic visit. Appropriate sources of this information include participant (or significant other) report, current pharmacy action profiles, and verification of medications documented in the medical record.

In the standard comparison group, labetalol treatment will be started only for BP ≥160/105. Only the lowest dose needed to give keep BP below this level will be given. Methyldopa or other clinically acceptable medication at the discretion of the clinical provider will be the third-line medication (after maximum tolerated doses of both labetalol and nifedipine ER) in the unlikely situation that a third medication is needed.

4.5 Participant follow up

Research nurses trained and highly experienced in obstetric and perinatal outcomes abstraction at each center will be responsible for research data abstraction from patient medical records. Outcomes will be ascertained until delivery and maternal/infant discharge. At hospital admission for delivery, maternal blood will be collected at the time of the admission lab work and will be processed for whole blood, plasma and serum samples. At delivery, cord blood will be collected and processed for future studies. These will include a comprehensive assessment of the role and interactions of clinical, biological and biophysical factors (e.g., BP levels, maternal obesity, smoking, glucose intolerance, hyperlipidemia, genes/pharmacogenetics and ultrasound findings) on the occurrence and severity of adverse outcomes including preeclampsia and fetal growth restriction. The placenta will be collected as part of clinical routine and sent to hospital pathology lab for sampling and analysis. Specimens will be frozen and shipped in batches to the UAB Ob/Gyn Diagnostic and Research Lab for storage.

After hospital discharge, participants will be followed up postpartum at 6 (4-12) weeks to ascertain maternal and infant status including readmissions and ER or unscheduled visits. The records of any ER visits or hospitalizations will be obtained for review.

In the active treatment group, the goal blood pressure will remain <140/90 for at least two weeks postpartum. The selection of medication may be based on clinical history, prepregnancy regimen and providers' preference. Participants in the standard care per ACOG (no treatment) arm may be initiated on antihypertensive therapy postpartum per their primary provider; choice of antihypertensive is left to their provider. CHAP will provide study medication when treatment is per protocol (i.e. prescription for labetalol or nifedipine to achieve blood pressure *<140/90 for active treatment*; prescription for labetalol or nifedipine to achieve blood pressure *<160/105 for no treatment arm*). The follow-up assessment will include items to assess adherence to antihypertensive therapy since delivery.

It is anticipated that by the end of the postpartum period most patients will be continued on labetalol or nifedipine ER, resume taking their usual prepregnancy medication, or be started/continued on an appropriate BP medication regimen by their clinical provider, taking into consideration their BP, co-morbidities, medication cost and future plans. Postpartum adherence, BP control and intervening clinical visits will be assessed by the study team at the 6 (4-12) week follow up visit.

Longer follow-up is anticipated as part of a separate follow-up study for which funding will be sought. This may include an interim phone visit at 6 months and in-person visits at 5 years to ascertain long-term maternal and child outcomes.

4.6 Adverse event reporting

The CHAP trial is testing whether antihypertensive medication used in pregnancy to maintain BP <140/90, compared with ACOG recommendation (no treatment), for uncomplicated mild CHTN reduces the frequency of important adverse outcomes associated with CHTN including 1) a severe composite outcome (perinatal death, placental abruption, severe preeclampsia and indicated preterm birth <35 weeks) and 2) SGA - a safety outcome. It is not a study of specific anti-hypertensive agents. The antihypertensive agents provided by the trial have been approved by the Food and Drug Administration (FDA), are routinely prescribed for lowering BP and are commonly used in pregnant women as part of clinical routine to treat BP when indicated.

Patient safety will be carefully monitored. Each participating investigator has primary responsibility for the safety of the individual participants under his/her care. In addition, an independent Data and Safety Monitoring Board (DSMB) will have primary responsibility for monitoring the accumulating study data for signs of adverse trends in morbidity/mortality and treatment-related serious adverse events. The DSMB will be appointed by the sponsor (NIH/NHLBI) and will comprise clinical scientists with expertise in Statistics/Epidemiology, Obstetrics, Neonatology and Internal Medicine/Cardiology.

An adverse event (AE) is defined as any untoward or unfavorable medical occurrence in a human subject, including any clinically significant abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Sites will report all serious SAEs and selected AEs to the Data Coordinating Center.

Consistent with NHLBI guidelines and OHRP policy, SAEs are adverse events that meet any of the following criteria:

- fatal or life-threatening
- result in significant or persistent disability,
- require or prolong hospitalization,
- result in a congenital anomaly/birth defect, or
- are important medical events that investigators judge to represent significant hazards or harm to research participants.

Specifically, any AE that meets any of these criteria (maternal death, ICU admission stroke, myocardial infarction, cardiomyopathy; fetal death or neonatal death) will be documented and reported as an SAE.SGA as a study outcome will also be a monitored AE, but not reported as an SAE, as these will be determined using appropriate birth weight and GA curves. In addition, any unexpected event which the investigator believes to have been caused or contributed to by the intervention, regardless of whether it resulted in hospitalization, will also be considered an AE or SAE (e.g., severe allergy or anaphylaxis suspected to be due to the patient's BP medication). Other AEs include maternal bradycardia, hypotension (BP< 100/60), syncope, stroke, renal failure, heart failure and may include neonatal hypoglycemia, hypotension and bradycardia unrelated to prematurity or diabetes mellitus.

Participants will be queried for SAEs and selected AEs at each prenatal clinic visit and patients admitted to the hospital will be monitored for these events.

4.7 Study Outcome Measures and Ascertainment

4.7.1 Primary outcomes:

1. A composite outcome **(Effectiveness)** including at least one of:
   a) Fetal or neonatal death,
   b) superimposed preeclampsia with severe features up to two weeks postpartum ;
   c) placental abruption, or
   d) indicated PTB <35 weeks (i.e. not due to spontaneous preterm labor or membrane rupture).

The definition of preeclampsia with severe features is as follows:

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)].

To be included in the primary outcome, abruptio placenta is defined as 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.

This primary outcome drives all key sample size considerations. This composite outcome is a measure of severe outcomes related to preeclampsia or CHTN; similar outcomes have been used in other trials, including the NICHD MFMU CAPPS and High Risk Aspirin trials.[9,61] Outcomes will be adjudicated through an independent centralized review familiar to our group.

2. Poor fetal growth (i.e. SGA<10th percentile based on birth weight): We will also examine SGA <5th percentile. SGA is not included in the composite because of concerns that therapy may be a cause (impaired placental blood flow). This is the primary safety outcome to evaluate harms. *Based on our preliminary data, however, BP control may be associated with a reduction in risk of SGA*. A national standard weight curve such as Alexander's or any other acceptable customized curve will be used to identify SGA infants.

4.7.2 Major secondary outcomes

1) Composite maternal cardiovascular and other morbidity: Death, any new heart failure, stroke or encephalopathy, MI/angina, pulmonary edema, ICU admission/intubation, encephalopathy, or renal failure.
2) Persistent severe maternal hypertension (with or without proteinuria) + components of the primary composite endpoint
3) Preterm birth and Indicated preterm birth (<37 weeks)
4) Composite of severe neonatal morbidities: Bronchopulmonary dysplasia (BPD), Retinopathy of prematurity (ROP), Necrotizing enterocolitis (NEC), Intraventricular hemorrhage (VH) grade III/IV.

The following outcomes will be evaluated in secondary studies:

5) Timing of delivery outcomes: The risks of 3 key outcomes, a) perinatal death, b) composite neonatal morbidity and c) composite of severe maternal morbidity (defined above) will be examined in relation to gestational age (completed weeks from 36 to 40 weeks) using longitudinal analysis methods to determine the delivery gestational age at which risks nadir (see analysis section).
6) Biospecimen collection: i) Maternal whole blood, plasma, paxgene and serum at the time of randomization and midtrimester (24-30 weeks), ii) cord blood (whole blood, serum and plasma) at time of delivery, iii)

placenta collected and sent to pathology for routine clinical evaluation. All maternal and cord blood specimens will be frozen at -80 degrees C for future studies.

7) These future biospecimens studies will include a comprehensive assessment of the role and interactions of clinical, biological and biophysical factors (e.g., BP levels, maternal obesity, smoking, glucose intolerance, hyperlipidemia, genes/pharmacogenetics and ultrasound findings) on the occurrence and severity of preeclampsia, SGA and other outcomes.
8) Adherence to treatment at 6 (4-12) weeks postpartum: The follow-up questionnaire will include items to assess adherence to antihypertensive therapy since delivery.

4.7.3 Other maternal outcomes

1. Superimposed Preeclampsia (mild or severe including eclampsia)
2. Superimposed gestational hypertension (persistent hypertension above baseline without proteinuria occurring after 20 week's gestation).
3. Serial maternal systolic and diastolic BP (mean values and changes during pregnancy should differ between groups if the intervention is successful). Both the pragmatic clinic and standardized automated/Omron BPs will be assessed.
4. Severe hypertension (treatment needed)
5. Cesarean delivery
6. Blood transfusion (during pregnancy or postpartum)

4.7.4 Other newborn outcomes:

1) NICU admission and stay
2) Low birth weight (<2500g)
3) Ponderal index (wt/ht^3)
4) Head circumference
5) Placental weight
6) Hypoglycemia
7) Bradycardia
8) Hypotension
9) Other neonatal morbidities (including respiratory distress syndrome, transient tachypnea of the newborn intubation/ventilation, seizures, hyperbilirubinemia, 5-min Apgar score <7and sepsis)

4.7.5 Health care resource utilization outcomes (these will be reported in secondary studies):

1) Prenatal clinic/ER visits
2) Prenatal hospitalizations
3) Delivery hospital stay (maternal/newborn)
4) Postpartum unscheduled/ER visits

5) Postpartum hospitalizations

4.7.6 Follow-up and Outcome Ascertainment Periods:

The primary outcomes will be ascertained from randomization until discharge from the delivery hospitalization and two weeks postpartum. For newborns who are not discharged from the hospital, neonatal death will be ascertained until 90 postnatal days. Secondary and other maternal/infant outcomes including BP control, treatment adherence, readmissions and ER/unscheduled visits and related diagnoses will be measured at a 6 week (4-12 weeks) postpartum visit. Records of such encounters will be obtained for review.

Planned long-term follow-up: We will plan for participants to be contacted by phone at 6 months to ascertain maternal and infant status. This phone contact will also facilitate anticipated follow-up study of the trial cohort (involving in-person visits annually) to determine long-term maternal and infant outcomes in relation to anti-hypertensive therapy during pregnancy. Key maternal outcomes include BP control, treatment adherence and cardiovascular outcomes; infant/child outcomes for such a separate study would include growth, neurodevelopment and metabolic outcomes by treatment status.

Central review of outcomes: Coordinated by the DCC and an outcomes adjudication committee, 2-3 site PIs will conduct a blinded record review and validation of findings for all patients reported or suspected of having the primary and selected major secondary outcomes.

5 Statistical considerations

5.1 Sample size for Primary outcome

The original sample size for the study (n=4700) was based on the rationale provided in section 5.1.1 below. A proposal to reduce the sample size for the primary outcome was initiated in 2016. The proposal was based on an evaluation of primary outcomes of the first 800 consecutive patients enrolled in the study, and based on a blinded sample size reassessment (SSR). The sample size based on this SSR was formally reduced to 2404 in December, 2018. The rationale is provided in section 5.1.2 below.

5.1.1 Original Sample Size

We used data from the MFMU Network's High Risk Aspirin study[9,11] (enrollment into the CHTN group was based on pragmatic clinic BPs) to estimate the frequency of the composite outcome components among 763 women with mild CHTN at baseline as follows: Fetal or neonatal death = 6.16%; severe preeclampsia (severe hypertension and proteinuria, eclampsia, preeclampsia with thrombocytopenia, creatinine>1.4, elevated liver enzymes) =0.66%; abruption =1.46%; indicated PTB <35 weeks =12.32%. **The frequency of the primary composite outcome was 16%.** Assuming a 2-sided alpha of 0.05 and conservative baseline incidence of 16% (since this is regardless of BP lowering therapy, and we expect the incidence to be higher in those not receiving therapy) the unadjusted sample sizes/arm needed to detect a 20-30% reduction in the primary outcome with 85-90% power are presented in Table 5. These unadjusted estimates do not take into account drop-ins and drop-outs or the interim look we propose. We assume: the 10% of the control group that will require treatment for severe hypertension are already well-accounted for in our baseline rate of 16% estimated from usual care; that in addition there will be up to a 10% rate of protocol violations (treatment in the control group without meeting criteria for severe hypertension) and that nonadherence in the treatment arm is 10%. The adjusted outcome rates for 25% reduction are: 15.6% and 12.4%, and the revised adjusted sample sizes/arm accounting additionally for 8% loss-to-follow up are presented in Table 5.

Table 5: Estimated sample size/arm (30%, 25% and 20% Reductions) under original plan

	30% REDUCTION		25% REDUCTION		20% REDUCTION	
Power	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
90%	**1075**	**1829**	**1587**	**2696**	**2539**	**4314**
85%	**919**	**1561**	**1356**	**2305**	**2170**	**3687**

The adjustment factors are based on studies of US populations. In one trial of therapy for mild CHTN, 10% of women in the control group required treatment for severe hypertension and treatment nonadherence or protocol violations occurred in 10%.[16] Our collective experience (mainly as sites of MFMU intervention studies) indicates treatment adherence rates of 80-90% among pregnant women and loss-to-follow-up rates of 5% or less.[16,61-62] **Therefore, 2350/arm or a total sample of 4700** will provide 85-90% power to detect at least a 2-sided 25% effect size for the primary outcome. The sample size is large, as desirable for a pragmatic trial.[63-65]The detectable

effect size will be 20% or less with >85-90% power if nonadherence, treatment crossover, protocol violations and losses to follow-up occur less frequently than anticipated. DSMB monitoring will allow us to stop early for benefit and safety, but only one formal interim look is planned at this time. **In addition, we propose an adaptive sample size: if the DSMB determines on interim review that a size larger than 4700 is needed, we will increase the sample size by up to 1000 based on their recommendation.*

5.1.2 Revised Sample Size

The original sample size was based on a 25% reduction in the primary composite outcome. Reductions as high as 30% and as low as 20% were also considered. At the time of the original protocol, the 30% reduction in the composite outcome rate was justified on the basis of other studies where reductions of 33% or greater were seen. However, these reductions were examined post hoc and from epidemiological studies and small trials. The original proposal also anticipated a high eligibility rate, estimating that 25% of screened patients would be enrolled. Thus, given these two factors a conservative 25% rate reduction was selected.

Based on studies published following the approval of the CHAP trial, it was hypothesized that the overall event rate for the CHAP study was underestimated along with the expected reduction in the primary outcome. In addition, participant accrual during the trial was slower than anticipated, arising from the underestimation of the yield from screening to randomization. A revised sample size (n=2404) was proposed that incorporated a larger 33% reduction in the primary outcome and thus reflected a more feasibly attainable target sample size. The total sample size of 2404 reflects a 33% reduction in the primary outcome (from a baseline rate of 16%), 10% noncompliance and crossover, and 85% power. As seen in Table 6 below, the necessary sample size per group is 1142 when incorporating these criteria; accounting for 5% attrition inflates the sample size per group to 1202 (n=2404 total).

Table 6: Estimated sample size/arm (33%, 30% and 25% Reductions) under revised plan as of January 2019

	33% REDUCTION		30% REDUCTION		25% REDUCTION	
Power	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
90%	**868**	**1336**	**1075**	**1829**	**1587**	**2696**
85%	**748**	**1142**	**919**	**1561**	**1356**	**2305**

Based on this revised sample size, it was decided to perform a blinded SSR based on the overall study composite outcome rate and assumptions as noted above. The blinded SSR examined internal study data in order to evaluate whether assumptions used for the original sample size were consistent with an underestimated composite outcome rate and whether the revised minimum target sample size of 2404 was sufficient. Complete details are provided in a separate Statistical Analysis Plan (SAP) and details are part of records of the December

2018 DSMB Report. Briefly, the overall event rate was determined by evaluating the primary outcome event rate in first 800 women enrolled into the trial. A 95% confidence interval for this composite outcome rate was also determined. Rates by study group were not examined in order to maintain the blinded SSR and avoid repeated statistical testing and inflation of the overall alpha level. The DCC estimated the event rates in the two combined trial groups based on the observed overall rate and under multiple hypothesized rate reductions. In addition, the DCC estimated the event rates in the two trial groups based on the lower bound of the 95% confidence interval for the overall rate and under multiple hypothesized rate reductions. This allowed data accrued early in the trial to provide a range of plausible event rates observable during the trial. Sample sizes needed to achieve at least 85% power based on these rates were then evaluated and compared with the proposed minimum sample size of 2404.

The formal SSR was performed and presented to the DSMB and NHLBI in 2018. In order to preserve confidentiality and any potential impact on equipoise, the actual numbers presented are withheld from this report (but they are intended to be published in a manuscript describing the study's design when enrollment is complete). In summary, the overall event rate was higher than that originally expected and the derived event rate in the untreated group was estimated to be higher than the 16% originally hypothesized. Furthermore, it was determined that the revised sample size of 1202 per group (n=2404 total) would indeed provide at least 85% power for the primary outcome for reductions as low as 25%.

5.2 Power for other outcomes

The sample size of 2404 provides adequate power to examine SGA and key secondary outcomes. The corresponding power for each outcome considering conservative estimates of baseline incidence and effect sizes given a 2-sided alpha of 0.05 are shown in Table 7.

Table 7: Power – SGA and Secondary Outcomes

Outcome	Incidence	Effect size %	Power
SGA	**10-14%**	**35-40**	**≥85%**
Preeclampsia	**20%**	**25**	**>85%**
Cardiovascular	**4-6%**	**50**	**80-90%**
Preterm birth	**20%**	**25**	**>85%**
Perinatal death	**4-6%**	**50**	**80-90%**

The baseline risks of SGA, preeclampsia, preterm birth and perinatal death are likely to be higher considering the reviewed literature and our preliminary data--power may actually be higher. The incidence of the rare maternal cardiovascular outcome is not well characterized. This study will provide an estimate. Finally, regarding the repository, we anticipate collecting baseline and follow-up biospecimens (especially maternal and cord blood) on ≥80% (n=1920).

c) Baseline/covariate information: These will include demographics (age, parity, ethnicity, education, profession, payor), entry GA at entry, entry BP, duration of CHTN, treatment status on entry, prior preeclampsia, prior fetal death, BMI, smoking/alcohol/drug use.

5.3 Analysis Plan

A detailed analysis plan is described in a separate SAP. This section summarizes the main considerations for data analysis.

The key analyses for this study are the comparisons reflected by the primary and secondary aims; both intent-to-treat (as the primary) and a per-protocol approach will be used.

5.3.1 Primary Aims

Standard comparisons of characteristics between groups will be conducted at baseline. It is anticipated that the randomization scheme will balance the groups for these covariates (considering the large sample size) and they will not be adjusted for in the primary analyses. However, secondary analyses of relevant outcomes using regression adjustments will be implemented to account for any suggested confounding covariates that are unbalanced between study groups. The potential adjustment covariates include baseline BP level, race/ethnicity, smoking status, prior anti-hypertensive use (known CHTN), gestational age at baseline and weight. Per protocol analyses, which reflect adherence to antihypertensive therapy will be conducted in secondary analyses.

The primary analysis will compare the incidence of the composite outcome and SGA between the 2 study groups – a chi-square p-value and the RR and 95% CI (relative to ACOG comparison group) will be computed and followed up with a logistic regression comparison which will take into account the duration of therapy, GA at initiation of therapy and other covariates. Event free survival will be calculated using Kaplan Meier estimates and tested using a log rank test. Student's t-test comparisons of continuous outcomes (duration of hospital, NICU stay, etc.) will be conducted.

5.3.2 Secondary Aims

The secondary outcomes will be similarly compared. The incidence of each of the 3 outcomes for this aim (see 3.1.5 b ii) will be compared by completed weeks. To investigate the impact on the timing of delivery), longitudinal analysis of the full trial cohort with treatment arm as a key covariate, and completed gestational age (weeks 36-40) and their interaction as the independent variable will be implemented to assess the incidence of each of the 3 outcomes. The OR (95% CI) at each gestational age relative to 39 weeks will be computed and then adjusted for relevant covariate characteristics using logistic regression. Additional analyses will involve computing the adjusted OR and 95% CI for each outcome given delivery at a specific gestational age vs. at term. We will assess whether there is a gestational age beyond which waiting to deliver might be harmful.

5.3.3 Interim Monitoring

One formal interim analysis will be conducted when 50% (n=1202) of the total sample size (n=2404) has completed the study. The first 1202 consecutive women enrolled in the study will be reviewed for primary outcomes following their last study visits. All suspected primary outcomes will undergo review for adjudication. The 1202 for this interim analysis will include the 800 that were considered for the SSR. In order to maintain maximum power for the final analysis, and to simultaneously protect the overall type I error of the study we will implement a Lan-DeMets alpha spending function that follows O'Brien-Fleming boundaries.[66-67] The timing of this evaluation is chosen such that it will allow sufficient time for adding additional sites; complete regulatory requirements and allow them to actively participate in the trial with enrollment of the needed number of additional patients.

To summarize this approach, suppose that X_i^2 (i=1,2) represents the usual chi-square test statistic for the primary outcome at the i^{th} look (note that =2 corresponds to the final look), then at the interim look:

Reject H_0 if $X_1^2 > 9$ (i.e. $p < 0.0027$), and stop study for efficacy; otherwise, continue. And at the final look:

Reject H_0 if $X_i^2 > 3.87$ (i.e. $p < 0.0492$).

We do not propose a formal stopping rule for safety, but note the DSMB will continuously monitor for safety.

5.4 Sample Size Feasibility and Accrual

Timely sample size accrual is a critical goal for CHAP trial's success. An accrual plan with recruitment milestones has been submitted to the NHLBI. Furthermore, the ethnic distribution assures an over-representation of minorities compared to the general US birth population in 2011.[68] Considering that over 5000 women with CHTN deliver annually at consortium centers (and assuming that 75% present prior to 18 weeks, 70% are mild and meet other criteria, and only 40% consent to the trial), approximately 1080 women were originally expected to be enrolled each year. Actual accrual rates through the year 2018 show that the trial enrolls approximately 500 each year. The total sample size through the end of 2018 was 1478. Thus the sample size of 2404 can be enrolled through the year 2020. Thus the study can be completed in 6 years of funding considering start-up time (6 months), patient follow-up after completing recruitment (3 months excluding long-term follow-up) and data analysis (4-6 months). These data will be used to monitor center/site performance in relation to accrual milestones. The CHAP Executive Committee may choose to add centers and/or drop non-performing centers. New centers will be added without requiring a protocol modification.

6 Data Collection

6.1 Data Collection Forms

Data will be entered/collected on standardized forms listed below:

HP01: Screening and Randomization Data Form
HP02: Baseline Data Form
HP03: Prenatal Study Visit Form
HP04: Study Drug Dispensing Log
HP05: Labor and Delivery Data Form
HP06: Neonatal Outcome Data Form
HP07: Maternal 6-week PostPartum and Child Follow-up
HP08: Placental Pathology
HP09: Blood Specimen Lab Shipment log
HP10: PAXgene Lab shipment log
HP11: Blood Specimen Lab Receipt
HP12: PAXgene Lab Receipt
HP13: Unanticipated Maternal Admission, ER, or PP Clinic Visit
HP14: NICU Outcome Data
HP15: Adverse Event
HP16: Participant Status Form
HP17 Outcome Report
HP18 Central Adjudication

6.2 Data Entry System

Data entry will be via a HIPAA compliant web-based data entry system managed by the DCC. Clinical center staff will enter the data. There are various data edit and validity checks built into the system. A Data Manual produced by the DCC describes the system and its operation, including automated reporting and notification of SAEs. All data entry staff will be certified by the DCC prior to data entry for the study.

7 Study Organization and Administration

7.1 Organization and Funding

The study is funded by the NHLBI and conducted as a Collaborative Agreement between the NHLBI and the CHAP Trial Consortium comprising 16 or more clinical centers (and 30 or more hospitals) with the Clinical and Data Coordinating Centers at UAB Schools of Medicine (OBGYN) and Public Health (Biostatistics) respectively. Any new centers or sites will be added without requiring a protocol amendment (the site list in the CHAP Manual Of Operations will be updated accordingly).

7.1.1 CHAP Steering Committee

A steering committee (SC) that brings together the **multi-disciplinary DCC and the Clinical Center/Site** PIs and **NHLBI** Scientific and Program Officers will oversee **implementation** including: finalizing this clinical protocol, training and certification, monitoring recruitment, data coordination and quality control, DSMB recommendations and IRB-related issues. The SC will also make final decisions about data analysis and interpretation, secondary analyses, presentation at scientific meetings and publications (including authorship). Key investigators/members of the SC are shown in the Manual of Operations. The SC will meet every 3 months by teleconference and will hold an annual face-to-face meeting ideally to coincide with the SMFM Annual Meeting in February. Guidelines similar to those of the MFMU Network will be applied. Decisions will be made by consensus (preferably) or simple majority of voting members. The DCC, the CCC, each CHAP primary clinical center and the NHLBI shall each have one vote on the steering committee. Dr. William Andrews (Ob/Gyn Chairman at UAB) will be the Chairperson of the SC and will have tie-breaking vote when applicable.

Planned additional centers: As the need arises to maintain accrual additional centers or additional sites affiliated with current centers may be brought in to replace non-performing sites.

7.1.2. Sub-Committees

Several Sub-committees will conduct the work of the CHAP consortium for approval by the steering committee. In general, subcommittees will include about 9 investigators and/or coordinators from the NHLBI, the CCC, the DCC and selected centers/sites. A chair will be designated by the executive committee.

1. Executive Committee: An EC comprising the CCC PI, Research Administrator/Nurse Coordinator, DCC PI and Deputy, Project cardiologist, NHLBI Team (including Branch Chiefs, Program Officer, Project Scientist, Biostatistician and Grants administrators) and 1-2 Center PIs (on a rotating basis) will be responsible for coordinating the development of the study and day-to-day implementation based on decisions of the SC and will review enrollment data, protocol and patient adherence and data quality on a regular basis. A SC secretary attached to the CCC will assist with tracking and retrieval of decisions and clinical implementation action items. The DCC will have a similar system specific for data management issues.

2. Protocol (Design and Analysis) Subcommittee: Will finalize the study protocol and address any protocol changes during the duration of the study. In addition to the design, this committee will also finalize plans for data analysis and management including interim review and adaptive sample size plan submitted to the DSMB. The committee will also review and pre-approve any ancillary studies prior to presentation and approval by the steering committee. Membership: DCC (2), CCC (2), Project Cardiologist, NHLBI (2), Centers (2 PIs, 2NC), Neonatologist.
3. Publications Sub-committee: This subcommittee is charged with finalizing procedures for review and approval by the SC, and will review all publications, presentations, abstracts, and slides of the CHAP trial and any ancillary study results. The CC and this subcommittee will develop procedures to track the development of publications and presentations (P&P), as well as strategies for stimulating P&P productivity. Additionally, the CC will provide analyses for publications and presentations, and the study web site will provide P&P tracking reports and study presentations and publications. Membership: DCC (2), CCC (2), NHLBI (1-2), Centers (2 PIs, 1 NC)
4. Protocol Review Committee and Data and Safety Monitoring Board: Both committees will be appointed by the NHLBI following existing procedures.
5. Study Coordinators Sub-Committee: This subcommittee facilitates communication and collaboration among clinical sites and the Coordinating Centers. It focuses on recruitment, retention, adherence, and implementation issues, identifying problems early to promptly implement solutions. It will be made up of all coordinators at all centers and the DCC [CCC (1-2), DCC (1-2), Each primary center (1), NHLBI (1)]
6. Biorepository Sub-Committee: This Subcommittee will finalize procedures for biological sample collection, processing, shipping, storage, and analysis – as well as a blood drawing and aliquoting scheme to reflect the storage of specimens for future use. The subcommittee will oversee the implementation of appropriate specimen collection and will screen all ancillary proposals involving specimen collection prior to review by the protocol committee and steering committee. Membership: DCC (1-2), CCC (2), NHLBI (1-2), Centers (2 PIs, 1 NC); Bio-repository coordinator
7. Outcome adjudication committees: This will involve most investigators and coordinators working in subgroups to validate and adjudicate key study outcomes.
8. Safety Subcommittee: This subcommittee will review and address concerns about the safety of study participants that may arise during the course of the study. Concerns related to safety of study intervention, study medication or study procedures will be reviewed by the committee. Additionally, this committee will help triage issues raised by clinic IRBs that are related to safety and review any clinical practice issues that may arise. They may also review summaries of study data related to the overall safety of study participation, but not reported by treatment assignment, and develop related reports for or respond to concerns from the Data and Safety Monitoring Board. Membership: DCC (1), CCC (1-2), NHLBI (1), Centers (2 PIs, 1 NC)

8 Study Timelines

We anticipate completing the study in 6 years or 72 months including start-up (months1-6), enrollment (months 7-60), complete follow-up (13-66 months), finalize data management/primary analysis (months 60-72 overlapping). We will continue developing the clinical protocol, operations manual and IRB materials prior to funding, and these will be finalized within 3-4 months of protocol approval. Research staff training and clinical provider training will be initiated in months 3-5, in order for enrollment to start by month 7. There will be overlap in these activities as sites and centers start at different times. A sample accrual milestone plan is show in the table below and an updated version from January 2019 (including actual enrollments through December 2018) is in the next table. This will be used to monitor adequate enrollment of participants into CHAP (assuming a 6-year project period). Minimum enrollment quotas will be assigned to centers/sites taking into consideration these quarterly targets and center characteristics.

Table 8. Milestone accrual plan under original sample size

Calendar Year	1st Quarter Jan - Mar	2nd Quarter Apr - June	3rd Quarter July - Sep	4th Quarter Oct - Dec	Total
2014	0	0	(0)	Startup (0)	0
2015	Startup	0	10	50	60
2016	120	200	260	260	840
2017	280	290	270	260	1100
2018	280	290	275	260	1105
2019	280	290	275	260	1105
2020	270	220	0	0	490
Total	1230	1290	1090	1090	4700

Table 9. Milestone accrual plan under revised sample size

Calendar Year	1st Quarter Jan - Mar	2nd Quarter Apr - June	3rd Quarter July - Sep	4th Quarter Oct - Dec	Total
2014	n/a	n/a	n/a	Startup (0)	0
2015	Startup	Startup	9	50	59
2016	107	93	101	104	405
2017	134	117	112	140	503
2018	134	122	133	122	511
2019	125	125	125	125	500
2020	125	125	125	51	426
Total	625	582	605	592	2404

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A Pragmatic Multicenter Randomized Trial
Antihypertensive Therapy for Mild Chronic Hypertension during Pregnancy

CHRONIC HYPERTENSION AND PREGNANCY (CHAP) PROJECT
NIH/NHLBI Collaborative Project

NCT02299414

Statistical Analysis Plan (v2.2)

Prepared by

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Revised December 13, 2021

CHAP STATISTICAL ANALYSIS PLAN

1. INTRODUCTION

During pregnancy, chronic hypertension (CHTN) is the most common major medical disorder encountered, occurring in 2-6%. Often overlooked, the substantial negative effect of CHTN on pregnancy includes a consistent 3- to 5-fold increase in superimposed preeclampsia and adverse perinatal outcomes (fetal or neonatal death, preterm birth (PTB), small for gestational age (SGA) and placental abruption) and possibly a 5- to10-fold increase in maternal cardiovascular and other complications (death, cerebrovascular accident, pulmonary edema and acute renal failure). Mild CHTN (BP <160/110) contributes to a large proportion of these adverse outcomes. While antihypertensive treatment of CHTN is standard for the general population (to reduce death and severe cardiovascular and renal complications), it is uncertain whether treatment during pregnancy reduces maternal or fetal complications, and there are concerns that decreased arterial pressure may reduce fetal blood flow and cause poor fetal growth or small-for-gestational-age (SGA) infants. Some authorities, including the American College of Obstetricians and Gynecologists (ACOG) and American Society of Hypertension (ASH) recommend against starting or continuing antihypertensive therapy for mild CHTN in pregnant women, particularly if BP is <160/105-110 mmHg. The recommendation to withhold antihypertensive treatment in pregnancy conflicts with the broader public health goal to reduce BP in those with CHTN, but there is no evidence that discontinuing therapy during the brief period of pregnancy affects outcomes. As a result, in practice, some providers prescribe antihypertensive therapy during pregnancy while others do not. For over a decade, authorities have consistently called for well-designed and powered trials to delineate the benefits and risks of pharmacologic therapy for mild CHTN during pregnancy.

Our multicenter consortium will conduct the Chronic Hypertension and Pregnancy (CHAP) Project, a large pragmatic randomized trial with a primary aim to evaluate the benefits and harms of pharmacologic treatment of mild CHTN in pregnancy. Pregnant women (N=2404) with mild CHTN (<160/105 by) with or without prior antihypertensive treatment will be randomized to either primary therapy (with labetalol or nifedipine ER) or to ACOG standard treatment (antihypertensive medication only if BP≥160/105 mmHg). The participants will be followed until delivery and for 6-12 weeks postpartum (a separate long-term follow-up study is also planned).

The sample size of 2404 was revised from 4700 in December 2018 following a blinded sample size reassessment (details below) and review by the Data Safety and Monitoring Board (DSMB) and the NHBLI. A single interim analysis is scheduled after half of the total sample (n=1202) has been enrolled and completed the trial through the follow-up visit and any necessary outcome adjudication.

Throughout this document, we will use the following terminology to differentiate treatment groups:

Lower BP = The group randomized to primary therapy (with labetalol or nifedipine ER)
Standard BP = The group randomized to ACOG standard treatment

2. DESCRIPTIVE ANALYSES

Patient characteristics at baseline will be summarized by randomization group. The two study groups will be labeled as Lower (for primary BP lowering therapy with labetolol or nifedipine ER) and Standard (for ACOG standard treatment). For continuous variables, means/medians and standard deviations (or interquartile ranges) will be reported. To assess and/or identify covariates for which adjusted sensitivity analyses might be conducted, student t-tests will be used to compare means between study groups. Where appropriate, medians and quartiles will be reported and the Wilcoxon rank sum test will be used as an

alternative comparison procedure. Categorical measures will be presented as counts and percentages and will be compared using the χ^2 tests of association to identify potential group differences. For rare outcomes such that the χ^2 test of association is not appropriate, Fisher's exact test will be used. Balance overall is expected because of the large sample size and we expect approximately 5% to be different by chance, since we are not adjusting these baseline comparisons for multiple testing. Any group characteristics that are identified as statistically significantly different between the two groups at a 0.05 level of significance will be considered as covariates in multivariable models in subsequent analyses of the primary study outcome.

PRIMARY HYPOTHESIS

3.1. Primary Hypothesis #1: Impact of Blood Pressure Treatment on the Primary Outcome (a Composite of Key Adverse Maternal and Newborn Outcomes)

H_0: There will be no difference in the rate of the primary outcome (quantified by the composite outcome of adverse maternal and newborn outcomes) in CHAP participants treated in the Lower BP group therapy compared to participants treated in the Standard Group.

3.1.1. Primary Outcome: The primary outcome is a composite of the following items: fetal or neonatal death within 28 days, superimposed preeclampsia with severe features up to two weeks postpartum, placental abruption (as defined in the study protocol), or indicated preterm birth <35 weeks gestation (i.e., not due to spontaneous preterm labor or membrane rupture). The occurrence of 1 or more of these items will be considered an occurrence of the primary study outcome.

Outcomes will be adjudicated by an adjudication committee made of a rotating group of study investigators masked to the treatment assignment. Two adjudicators will conduct a blinded record review of all patients reported or suspected of having any component of the primary composite outcome and selected major secondary outcomes. Each site will provide the DCC with a set of materials necessary for the review through the electronic data entry system (eDES). These materials follow a uniform checklist of items regardless of the type of outcome under review, and are collected after the patient has completed participation in the study (e.g., after the 6-week follow-up visit). The DCC will then review the materials for completeness and redaction of any personally identifiable information and indicators of treatment assignment. The DCC will subsequently provide the reviewers with those materials. The 2 adjudicators for each study patient are randomly selected (the patient and adjudicator cannot be from the same site). Agreement between the adjudicators is needed to complete the process. A 3rd reviewer will be assigned only if needed.

3.1.2. Analysis Plan: This hypothesis examines the effectiveness of structured blood pressure treatment (Lower BP group) for mild chronic hypertension in pregnancy versus usual care (Standard BP group). The χ^2 test of association will be used to evaluate whether the rate of the primary outcome differs between the two blood pressure management approaches. The primary analysis will follow 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 is undetermined (for example, dropout prior to delivery), the primary analysis will utilize multiple imputation for the primary outcome. Missing values will be estimated using characteristics within each treatment group that may be predictive of the composite outcome. Specifically, a logistic regression model will be fit 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 $\geq$ 150 and/or DBP $\geq$ 100). Multiple imputed data sets will be developed and up to 5 replicates will be considered. The primary analysis will be conducted on each of the imputed complete data sets and the final results will be pooled.

A sensitivity analysis will include all individuals for whom a primary outcome can be assessed (a complete-case analysis) in a modified ITT approach. Our expectation is that on a small fraction (<10%) of the dataset will require imputation and thus the complete case analysis will agree substantially with the primary imputation-based analysis.

Risk ratios (RR) and 95% confidence intervals (CIs) will be computed and presented, as well as individual group rates and 95% CIs. Standard comparison of the covariate characteristics at baseline between study groups will be undertaken (Section 2) to assess the randomization balance on measured covariates. Tests of significance will be two-sided and evaluated at the 0.05 level of significance. Since the sample size for CHAP is large, it is unlikely that "important" covariates (such as race, BMI or age) will be imbalanced through the randomization process. However, in the unlikely event that this occurs, adjustment for covariates will be made by modeling the log-odds of the outcome using multivariable logistic regression including terms indicating group membership, site and each of the imbalanced covariates. In other words, the log-odds of the primary outcome for any individual will be modeled using the following form:

$$\ln\left(\frac{P(outcome)}{1-P(outcome)}\right) = \beta_0 + \beta_1 x_1 + \sum \beta_j z_j.$$

Above, $x_1 = 1$ if the patient is in the Lower BP group (treatment) and equals 0 if the patient is in the Standard BP group (no-treatment). The set of z_j's consists of all covariates in the model including site. Hence, under this model, the term β_1 represents the difference in the log-odds between the two groups. To address the hypothesis of interest for primary hypothesis #1, we will perform a statistical test of H_0: $\beta_1 = 0$ vs. H_1: $\beta_1 \neq 0$. Quantification of the treatment effect will be performed by exponentiation of the estimated coefficient, $\exp(\beta_1)$, to obtain an estimate of the odds ratio. The confidence interval will be determined similarly. The presence of a homogeneous center effect will be examined with inclusion of study center as strata using the Breslow-Day test. Generalized estimating equations to account for repeated measures within sites may be considered as well, especially in the event that significant center effects are detected. Modified Poisson regression modeling with robust standard errors will also be considered in order to estimate risk ratios for the primary outcome while adjusting for any possible covariates. While logistic regression yields odds ratios that often approximate risk ratios, direct modeling of risk ratios may yield more informative estimates of the true risk of the outcome.

Sensitivity analyses will be performed as described above. Supplementary analyses will consider best-case and worst-case scenarios. Specifically, we will consider all missing outcomes in the Lower group to be non-outcomes and those in the Standard group to be outcomes. The reverse will also be considered, where all missing outcomes in the Lower group will be outcomes and those in the Standard group will be non-outcomes. Consistency of effect estimates and statistical significance will be examined across all analytic approaches.

3.1.3. Original Sample Size for Primary Outcome: We used data from the MFMU Network's High Risk Aspirin study (enrollment into the CHTN group was based on pragmatic clinic BPs) to estimate the frequency of the composite outcome components among 763 women with mild CHTN at baseline as follows: Fetal or neonatal death = 6.16%; severe preeclampsia (severe hypertension and proteinuria, eclampsia, preeclampsia with thrombocytopenia, creatinine>1.4, elevated liver enzymes) =0.66%; abruption =1.46%; indicated PTB <35 weeks =12.32%. The frequency of the primary composite outcome was assessed as 16%. Assuming a 2-sided alpha of 0.05 and conservative baseline incidence of 16% (since this is regardless of BP lowering therapy, and we expect the incidence to be higher in those not receiving therapy) the unadjusted sample sizes/arm needed to detect a 20-30% reduction in the primary outcome with 85-90% power are presented in Table 1. These unadjusted estimates do not take into account drop-ins and drop- outs or the interim look we propose. We assume: the 10% of the control group that will require treatment for severe hypertension are already well-accounted for in our baseline rate of 16% estimated from usual care; we assume there will be up to an additional 10% rate of protocol

violations (treatment in the Standard BP group without meeting criteria for severe hypertension) and that nonadherence in the Lower BP group is 10%. The adjusted outcome rates for 25% reduction are: 15.6% and 12.4%, respectively and the adjusted sample sizes/arm accounting additionally for 8% loss-to-follow up are presented in Table 1.

Table 1: Estimated sample size/arm (30%, 25% and 20% Reductions) under original plan

	30% REDUCTION		25% REDUCTION		20% REDUCTION	
Power	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
90%	**1075**	**1829**	**1587**	**2696**	**2539**	**4314**
85%	**919**	**1561**	**1356**	**2305**	**2170**	**3687**

The adjustment factors are based on studies of US populations. In one trial of therapy for mild CHTN, 10% of women in the control group required treatment for severe hypertension and treatment nonadherence or protocol violations occurred in another 10%. Our collective experience (mainly as sites of MFMU intervention studies) indicates treatment adherence rates of 80-90% among pregnant women and loss-to-follow-up rates of 5% or less. Therefore, 2350/arm or a total sample of 4700 will provide 85-90% power to detect at least a 25% reduction in the primary outcome using a 2-sided testing approach. The sample size is large, as desirable for a pragmatic trial. The detectable treatment effect will be 20% or less with >85-90% power if nonadherence, treatment crossover, protocol violations and losses to follow-up occur less frequently than anticipated.

DSMB monitoring will ensure safety for the participants and may allow us to stop early for safety, which provides for a benefit in one of the treatment arms. Given the duration of the trial up to 5 active years and the need for the DSMB to assess safety at least once per year (and likely at least twice per year), we have up to 5 formal interim analyses planned at this time. **In addition, we propose an adaptation of the proposed sample size: if the DSMB determines on interim review that a size larger than 4700 is needed based on an overestimate of the outcome event rate in the Standard BP group, we will increase the sample size by up to 1000 based on their recommendation.*

3.1.4 Revised Sample Size for Primary Outcome as of January 2019: The original sample size was based on a 25% reduction in the primary composite outcome, and reductions as high as 30% and as low as 20% were also considered. At the time of the original protocol, the 30% reduction in the composite outcome rate was justified on the basis of other studies where reductions of 33% or greater were seen. However, these reductions were examined post hoc and from epidemiological studies and small trials. The original proposal also anticipated a high eligibility rate, estimating that 25% of screened patients would be enrolled. Thus, given these two factors a conservative 25% rate reduction was selected.

Based on studies published following the approval of the CHAP trial, it was hypothesized that the overall event rate for the CHAP study was underestimated along with the expected reduction in the primary outcome. In addition, participant accrual during the trial was slower than anticipated, arising from the underestimation of the yield from screening to randomization. A revised sample size (n=2404) was proposed that incorporated a larger 33% reduction in the primary outcome and thus reflected a more feasibly attainable target sample size. The total sample size of 2404 reflects a 33% reduction in the primary outcome (from a baseline rate of 16%), 10% noncompliance, 10% crossover, and 85% power. As seen in Table 2 below, the necessary sample size per group is 1142 when incorporating these criteria; accounting for 5% attrition inflates the sample size per group to 1202 (n=2404 total).

Table 2: Estimated sample size/arm (33%, 30nd 25% Reductions) under revised plan as of January 2019

	33% REDUCTION		30% REDUCTION		25% REDUCTION	
Power	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
90%	868	1336	1075	1829	1587	2696
85%	748	1142	919	1561	1356	2305

Based on this revised sample size, it was decided to perform a blinded SSR based on the overall study composite outcome rate and assumptions as noted above. The blinded SSR examined internal study data in order to evaluate whether assumptions used for the original sample size were consistent with an underestimated composite outcome rate and whether the revised minimum target sample size of 2404 was sufficient. Complete details are provided in a separate SSR and Interim Analysis plan and details are part of records of the December 2018 DSMB Closed Report. Briefly, the overall event rate was determined by evaluating the primary outcome event rate in first 800 women enrolled into the trial. A 95% confidence interval for this composite outcome rate was also determined. Rates by study group were not examined in order to maintain the blinded SSR and avoid repeated statistical testing and inflation of the overall alpha level. The DCC estimated the event rates in the two combined trial groups based on the observed overall rate and under multiple hypothesized rate reductions. In addition, the DCC estimated the event rates in the two trial groups based on the lower bound of the 95% confidence interval for the overall rate and under multiple hypothesized rate reductions. This allowed data accrued early in the trial to provide a range of plausible event rates observable during the trial. Sample sizes needed to achieve at least 85% power based on these rates were then evaluated and compared with the proposed minimum sample size of 2404.

The formal SSR was performed and presented to the DSMB and NHLBI in 2018. In order to preserve confidentiality and any potential impact on equipoise, the actual numbers presented are withheld from this report (but they are intended to be published in a manuscript describing the study's design when enrollment is complete). In summary, the overall event rate was higher than that originally expected and the derived event rate in the untreated group was estimated to be higher than the 16% originally hypothesized. Furthermore, it was determined that the revised sample size of 1202 per group (n=2404 total) would indeed provide at least 85% power for the primary outcome for reductions as low as 25%.

3.2. Primary Hypothesis #2: Impact of Blood Pressure Treatment on Poor Fetal Growth (i.e. SGA<10th percentile based on birth weight)

H_0: There will be no difference in the rate of poor fetal growth in CHAP participants treated in the Low BP group therapy compared to participants in the Standard BP group.

3.2.1. Poor Fetal Growth Outcome: We will examine small for gestational age (SGA) infants identified as <10th percentile based on birth weight at the delivery gestational age. SGA has not been included in the composite, because the concerns that therapy may be a cause (impaired placental blood flow) of SGA, it is assessed separately as the primary safety outcome to evaluate harms. *The two primary hypotheses provide clear endpoints for benefit versus harm. Based on our preliminary data, however, BP control may be associated with a reduction in risk of SGA*. A national standard weight curve presently planned to be Alexander's, but may be modified prior to data closure with another acceptable customized curve used to identify SGA infants at the time of analysis. We will also, secondarily, examine extreme SGA <5th and <3rd percentiles.

3.2.2. Analysis Plan: The χ^2 test of association will be used to evaluate whether the rate of the SGA differs between the two blood pressure management approaches. The primary analysis will follow the

analysis plan for the composite primary outcome. Specifically, for cases where the primary composite outcome is undetermined (for example, dropout prior to delivery), the primary analysis will utilize multiple imputation based on the characteristics within treatment group that are predictive of the SGA outcome. Logistic regression models will be fit within treatment group using baseline characteristics predictive of the SGA outcome and this group-specific model will be used to provide the imputed outcome values. Up to 5 replicates will be considered. All individuals will be analyzed as randomized to the two treatment groups, regardless of whether they adhered to their assigned treatment. Sensitivity analyses will follow the primary outcome analysis plan described above. Relative rates (RR) and 95% confidence intervals (CIs) will be computed and presented, as well as individual group rates and 95% CIs. In the event of imbalanced patient characteristics in the two groups, multivariable modeling will be performed as described in the previous section.

3.2.3. Power for other outcomes: The sample size of 2404 provides adequate power to examine SGA and key components of the primary outcome separately. The corresponding power for each outcome considering conservative estimates of baseline incidence and effect sizes given a 2-sided alpha of 0.05 are shown in Table 3.

Table 3: Power – SGA and Secondary Outcomes

Outcome	Incidence	Effect size %	Power
SGA	**10-14%**	**35-40**	**≥85%**
Preeclampsia	**20%**	**25**	**>85%**
Cardiovascular	**4-6%**	**50**	**80-90%**
Preterm birth	**20%**	**25**	**>85%**
Perinatal death	**4-6%**	**50**	**80-90%**

The baseline risks of SGA, preeclampsia, preterm birth and perinatal death are likely to be higher considering the literature reviewed and our preliminary data, thus power may actually be higher. The incidence of the rare maternal cardiovascular outcome is not well characterized. This study will provide a more precise estimate and will consider any new heart failure, stroke or encephalopathy, and MI/angina as cardiovascular outcomes.

3.3 Interim Monitoring: The study investigators, in conjunction with the study DSMB and NHLBI, propose 1 interim analysis for the CHAP trial. In order to maintain maximum power for the final analysis, and to simultaneously protect the overall type I error of the study, we propose that alpha levels at the interim analysis be selected using a Lan-DeMets alpha spending function that follows O'Brien-Fleming boundaries.

The formal interim analysis will be conducted when 50% (n=1202) of the total sample size (n=2404) has completed the study. The first 1202 consecutive women enrolled in the study will be reviewed for primary outcomes following their last study visits. All suspected primary outcomes included in the composite primary outcome will undergo review for adjudication. The interim analysis will focus on the analysis of these adjudicated outcomes. Group totals and rates will be presented in a masked fashion (using A and B labels rather than actual treatment assignment labels), where only the study statistician will know the true identity of A and B. The masked labels will be removed and true group assignments revealed only upon request by the DSMB.

The 1202 for this interim analysis will include the 800 that were considered for the SSR. In order to maintain maximum power for the final analysis, and to simultaneously protect the overall type I error of the study we will implement a Lan-DeMets alpha spending function that follows O'Brien-Fleming boundaries. The timing of this evaluation is chosen such that it will allow sufficient time for adding

additional sites; complete regulatory requirements and allow them to actively participate in the trial with enrollment of the needed number of additional patients.

To summarize this approach, suppose that X_i^2 (i=1,2) represents the usual chi-square test statistic for the primary outcome at the i^{th} look (note that i =2 corresponds to the final look), then at the interim look:

Reject H_0 if $\chi_1^2 > 9$ (i.e. $p < 0.0027$), and stop study for efficacy; otherwise, continue.

And at the final look:

Reject H_0 if $\chi_i^2 > 3.87$ (i.e. $p < 0.0492$).

We do not propose a formal stopping rule for safety, but note the DSMB will continuously monitor for safety.

The interim analysis will include statistical significance testing only for the primary composite outcome, components of the primary outcome, and SGA <10th percentile.

4. Additional Analyses

For the primary outcome, both intent-to-treat (as the primary) and a per-protocol approach will be used. The per-protocol population will be defined as those individual in the Lower BP (treatment) group who have >80% compliance and attendance at all scheduled visits. No adjustments will be made in the Standard Group since this provides our pragmatic control group. Secondary analyses will be examined accounting for the duration of therapy, prior antihypertensive therapy, race/ethnicity, pre-existing diabetes, GA at initiation of therapy and other covariates.

Pre-pregnancy and/or early pregnancy BMI will be evaluated for possible effects on all outcomes. Sensitivity analyses will be conducted to examine these possible effects. We will also evaluate potential interactions between BMI and treatment assignment. Subgroup analyses (by BMI class) will be explored where warranted. Similar interactions with other key patient characteristics will be examined.

Event free survival for the first occurrence of any of the primary outcome composite variables and will be calculated using Kaplan Meier estimates with testing via a log rank test. Student's t-test for comparisons of continuous outcomes (duration of hospital, NICU stay, etc.) will be conducted as well as regression analyses adjusting for pertinent covariates.

4.1 Secondary Aims/Hypotheses: Secondary outcomes will be compared using methods and approaches outlined above. The incidence of each of the 3 outcomes for this aim (perinatal death, composite neonatal morbidity, and composite of severe maternal morbidity) will be compared by completed weeks. To investigate the impact on the timing of delivery, longitudinal analysis of the full trial cohort with treatment arm as a key covariate, using completed gestational age (weeks 36-40) and their interaction as the independent variable will be implemented to assess the incidence of each of the 3 outcomes. The OR (95% CI) at each gestational age relative to 39 weeks will be computed and then adjusted for relevant covariate characteristics using logistic regression. Additional analyses will involve computing the adjusted OR and 95% CI for each outcome given delivery at a specific gestational age vs. at term. We will assess whether there is a gestational age beyond which waiting to deliver might be harmful.

4.2 Major secondary outcomes

4.2.1 Secondary Hypothesis #1: Impact of Blood Pressure Treatment on Maternal Cardiovascular and Other Morbidity

H_0: There will be no difference in the maternal cardiovascular and other morbidities in CHAP participants treated in the Lower BP group therapy compared to participants treated in the Standard Group.

4.2.2. Maternal Cardiovascular and Other Morbidity Outcomes: The endpoint for this analysis will be a composite outcome of maternal cardiovascular and other morbidities. The composite will include maternal death, any new heart failure, stroke or encephalopathy, MI/angina, pulmonary edema, ICU admission/intubation, encephalopathy, or renal failure. The occurrence of 1 or more of these items will be considered an occurrence of this important secondary study outcome.

4.2.3. Neonatal Outcomes: In addition to SGA (described above), we will examine differences in key neonatal outcomes between study groups. Specifically, we will compare rates of NICU admission and length of stay.

4.3. Other monitored maternal and neonatal outcomes: The list below identifies secondary and tertiary items that will be evaluated at the time of the primary analysis and presented with the primary results.

1) Persistent severe maternal hypertension (with or without proteinuria) + components of the primary composite endpoint
2) Preterm birth and indicated preterm birth (<37 weeks)
3) Composite of severe neonatal morbidities: Bronchopulmonary dysplasia (BPD), Retinopathy of prematurity (ROP), Necrotizing enterocolitis (NEC), Intraventricular hemorrhage (VH) grade III/IV.
4) Superimposed Preeclampsia (mild or severe including eclampsia)
5) Superimposed gestational hypertension (persistent hypertension above baseline without proteinuria occurring after 20 week's gestation).
6) Serial maternal systolic and diastolic BP (mean values and changes during pregnancy should differ between groups if the intervention is successful). Both the pragmatic clinic and standardized automated/Omron BPs will be assessed.
7) Severe hypertension (treatment needed)

4.4. Other monitored outcomes: The list below identifies individual outcomes that will be examined as secondary and tertiary outcomes following the study's primary analysis. Additional secondary analysis concepts may be submitted to the Publications Committee for review, feasibility assessment, and ranking/queueing. Procedures for submissions are available in the CHAP Publications Guidelines document.

8) Timing of delivery outcomes: The risks of 3 key outcomes, a) perinatal death, b) composite neonatal morbidity and c) composite of severe maternal morbidity (defined above) will be examined in relation to gestational age (completed weeks from 36 to 40 weeks) using longitudinal analysis methods to determine the delivery gestational age at which risks nadir (see analysis section).
9) Adherence to treatment at 6 (4-12) weeks postpartum: The follow-up questionnaire will include items to assess adherence to antihypertensive therapy since delivery.

Other maternal outcomes
1) Cesarean delivery
2) Blood transfusion (during pregnancy or postpartum)

Other newborn outcomes:

1) Low birth weight (<2500g)
2) Ponderal index (wt/ht^3)
3) Head circumference
4) Placental weight
5) Hypoglycemia
6) Bradycardia
7) Hypotension
8) Other neonatal morbidities (including respiratory distress syndrome, transient tachypnea of the newborn intubation/ventilation, seizures, hyperbilirubinemia, 5-min Apgar score <7 and sepsis)
9) SGA determined by current national standard nomogram vs. individualized nomogram for birth weight

Health care resource utilization outcomes:

1) Prenatal clinic/ER visits
2) Prenatal hospitalizations
3) Delivery hospital stay (maternal/newborn)
4) Postpartum unscheduled/ER visits
5) Postpartum hospitalizations