Tight control versus usual postpartum care following hypertensive disorders of pregnancy: a randomized controlled trial

Unique Protocol Identification Number:

National Clinical Trial (NCT) Identified Number:

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Statement of Compliance

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 Protocol Summary

1.1 Synopsis

Title: Feasibility of tight control versus usual postpartum care following hypertensive disorders of pregnancy: a randomized controlled trial

Study Description:

Objectives:	Primary Objective:	To assess the feasibility of conducting a randomized controlled trial of tight blood pressure control (<135/85 mmHg on home blood pressure monitoring) vs. standard of care (<150/100 mmHg on home blood pressure monitoring) in postpartum individuals following a hypertensive disorder of pregnancy (HDP).
	Secondary Objectives:	To assess the effect of tight blood pressure control on longer-term blood pressure control and postpartum care utilization to inform sample size for a subsequent large-scale randomized trial

Endpoints:	Primary Endpoint:	Proportions of individuals who are eligible, enroll, and remain in the study through 6 weeks postpartum (Target: >40% enrollment, >80% retention)
	Secondary Endpoints:	Mean arterial blood pressure, systolic blood pressure, and diastolic blood pressure at 6 weeks and 6 months postpartum at a research study visit. Proportion with stage 1 or greater hypertension at each study visit. Mean home blood pressures throughout first six weeks postpartum. Care utilization including postpartum emergency room visits, hospital readmissions, and outpatient office visits.
Study Population:		
Phase:	3	
Description of Sites/Facilities Enrolling Participants:	Single-center, tertiary care center	
Description of Study Intervention:	Tight blood pressure control defined as goal home blood pressure <135/85 via remote blood pressure monitoring for 6 weeks postpartum	
Study Duration:	6 months	

Participant Duration:	6 months

1.2 Schema

1.3 Schedule of Activities (SoA)

2 Introduction

2.1 Study Rationale

There are inconsistent clinical recommendations for management of postpartum hypertension. There is overwhelming evidence of benefit of lower BP targets in a non-pregnant population and in individuals with chronic hypertension in pregnancy.[22,23] Specifically for non-pregnant individuals, the American College of Cardiology (ACC) recommended BP threshold for initiation of an antihypertensive medication is 140/90 mmHg and even lower, 130/80 mmHg, for individuals at high risk for CVD. Recently, the Chronic Hypertension and Pregnancy (CHAP) trial found benefit in targeting a BP threshold of 140/90 mmHg for initiation of medications during pregnancy for individuals with chronic hypertension.[22] Despite this, ACOG continues to recommend a threshold of 150/100 mmHg for initiation of anti-hypertensive medications in the postpartum period.[9] This approach fails to consider the anticipated exacerbation of hypertension and is likely a contributor to hypertension-related maternal morbidity and mortality in the postpartum period.[24] Despite the inconsistent management recommendations, professional societies (including ACOG, ACC and Society for Maternal Fetal Medicine) recognize the public health significance and the need for a well-designed trial to evaluate the benefits and harms of tighter blood pressure control in the postpartum period.[9,27,28]

2.2 Background

Rising rates of cardiovascular disease (CVD) in women make it a major public health concern.[1] Despite this, women remain underrepresented in cardiovascular clinical trials relative to their percentage of the population and disease burden.[2] –4The urgency of these trends is amplified by the fact that chronic hypertension is a condition that increases more rapidly during the reproductive years with worse morbidity in females compared with males.[5] There are meaningful, sex-based differences in symptomatology and clinical outcomes of CVD in women.

Compared to men, women are diagnosed later, are less likely to receive guideline-concordant care and overall quality of care is significantly lower.[6,7] Collectively, these findings translate to stagnant mortality rates from CVD in women, particularly young women, and emphasize the importance of approaches that are centered on female-specific risk factors and target primary prevention.[6,8]

Women with hypertensive disorders of pregnancy progress rapidly to chronic hypertension in the first few years after delivery. The trajectory of blood pressure from HDP to chronic hypertension remains understudied and poorly understood. The prior clinical approach in obstetrics was that the pathogenesis of preeclampsia is resolved with delivery. This hands-off approach to management has likely contributed to the increasing maternal morbidity and mortality seen in the postpartum period. In the largest United States contemporary cohort of individuals (nuMoM2b/Heart Health Study), 37% of women with a hypertensive disorder of pregnancy developed chronic hypertension by 3 years postpartum.[10] In our pilot work of individuals with a hypertensive disorder of pregnancy and pre-pregnancy obesity, 58% developed stage 1 hypertension or greater by one-year after delivery. There is compelling evidence that the preponderance of HDP-associated CVD risk is linked to progression to chronic hypertension following pregnancy, yet the recovery of blood pressure and transition to chronic hypertension remains understudied.[10,21] Prevention in this population should target the critical time period of the first year after delivery.[16,17]

Recent evidence suggests the immediate postpartum period is a critical time for CV remodeling, with implications for long-term maternal health. Small RCTs have demonstrated that improved management of hypertension immediately postpartum leads to longer-term BP benefits.[29] In the SNAP-HT trial, done in the United Kingdom, self-managed of BP with home monitoring and tight BP control led to improved diastolic BP at 6 months postpartum that was sustained through 3-4 years after delivery in n=62 women**.** A similar proportion of women were on anti-hypertensive medications at 6 months postpartum across both arms, but tighter BP control during the critical immediate postpartum period led to lower BP long-term (-4.5 mmHg office diastolic BP at 6 months and -6.8 mmHg ambulatory diastolic BP at 3-4 years). Similarly, in our data, the proportion of BPs that are <140/90mmHg in the first six-weeks postpartum is associated with a lower risk of hypertension at one-year postpartum and lower relative wall thickness and LV remodeling (see preliminary data). We hypothesize that this benefit is secondary to improved CV remodeling during this critical period that results in long-term BP benefit that is sustained beyond the intervention period. In this application, we will directly test this hypothesis in an adequately-powered trial designed to assess the impact of tight postpartum BP control on long-term BP and cardiac remodeling.

Successful execution of a postpartum intervention trial requires established collaborations between high-risk obstetricians and cardiologists and can leverage existing, effective

infrastructure for home monitoring and retention postpartum. This line of research is distinctly at the intersection of high-risk obstetrics and cardiology. While trials conducted during pregnancy could be executed entirely within the context of prenatal care, our proposed study extends to 1 year postpartum and cannot be implemented fully within the care structure of solely an obstetrics or cardiology practice. Rather, to effectively study this critical question requires the collaborative infrastructure that we have successfully established at our institution. We have developed and enrolled over 9,000 women with HDP into a clinical postpartum remote hypertension management program, who have contributed >150,000 BPs in the first 6 weeks postpartum. We demonstrate high adherence, patient satisfaction, and a reduction in hospital readmission among our population (see preliminary data).[25,32,33] We have recently expanded this remote BP monitoring 6 week program to 1 year postpartum, housed within our highly successful multi-disciplinary postpartum hypertension clinic. Despite our program's success, at the conclusion, 30% of women still require anti-hypertensive medications, and at 1 year postpartum, 50% remain hypertensive. These peripartum BP trends likely contribute to an "unexplained epidemic" of increased CVD among young women, and suggest that further interventions may be necessary to improve hypertension and CV-related maternal morbidity following a HDP.

Cardiovascular disease (CVD) is the leading cause of death in women worldwide, and despite declines in all other age groups, mortality rates attributed to CVD are increasing in women of childbearing age. Hypertensive disorders of pregnancy (HDP), including preeclampsia and gestational hypertension, are female-specific conditions that are well-established risk factors for CVD across diverse patient populations. There is compelling evidence that the preponderance of HDP-associated CVD risk is linked to progression to chronic hypertension following pregnancy. The urgency of these trends is amplified by the fact that chronic hypertension is a condition that increases more rapidly during the reproductive years with worse morbidity in females compared with males. Understanding and mitigating progression to chronic hypertension in the postpartum period after a HDP may prevent CVD, a critical yet under-studied period of risk and an important opportunity for intervention to prevent chronic disease in women.

Hundreds of studies in non-pregnant or postpartum adults demonstrate that lower blood pressure reduces CV-related morbidity and mortality. However, the thresholds for postpartum anti-hypertensive medication initiation remains at 150/100 without change in over 30 years. HDP carry a high risk of persistent postpartum hypertension, with 20-30% still requiring antihypertensive medications at 6 weeks after delivery and up to 50% with chronic hypertension at one-year postpartum. While recent data from a multi-center randomized controlled trial (RCT) demonstrate that tighter BP control during pregnancy in individuals with mild chronic hypertension improves maternal and fetal outcomes, postpartum BP management is unstudied.

The current blood pressure thresholds for anti-hypertensive medication initiation for all adults, except pregnant and postpartum individuals is 140/90 mmHg in the clinic or 135/85 mmHg at

home. The American College of Obstetricians and Gynecologists recommends postpartum initiation of medication for persistent BP ≥150/100 mmHg, a much higher threshold for treatment than in non-pregnant or postpartum adults. These recommendations do not account for the expected exacerbation of hypertension that occurs at days 4-7 postpartum, which is associated with an increase in postpartum hospital readmission, severe hypertension and maternal morbidity. Small trials in the United Kingdom have shown that tight BP control during a critical period postpartum improves BP years postpartum. We have compelling observational data that higher BP (>140/90mmHg) in the first six weeks postpartum is associated with an increased risk of concentric left ventricular remodeling and development of chronic hypertension at one to two years postpartum. We have developed and implemented a clinical postpartum remote hypertension management program that has enrolled over 9000 of individuals with HDP who deliver in our hospital system since 2018. We plan to leverage this robust, well-established infrastructure to conduct an urgently needed randomized trial to generate definitive evidence on appropriate BP treatment thresholds in the postpartum period following a hypertensive disorder of pregnancy to prevent chronic hypertension and other cardiovascular sequelae.

The overall objective of this study is to assess the feasibility of conducting a single-site RCT within our remote BP management program of tight BP control versus usual care in the immediate postpartum period through 6 months in individuals with a HDP.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

- Symptomatic hypotension
- Possible decrease in breastmilk supply impacting breastfeeding continuation

2.3.2 Known Potential Benefits

- Possible lower rates of progression to chronic hypertension
- Possible reduction in healthcare utilization postpartum

2.3.3 Assessment of Potential Risks and Benefits

3 Objectives and Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
	Is a randomized controlled trial of tight blood pressure control (<135/85 mmHg on home blood pressure monitoring) vs. standard of care (<150/100 mmHg on home blood pressure monitoring) in postpartum individuals following a hypertensive disorder of pregnancy (HDP) feasible? *We hypothesize that average enrollment will represent 10 participants per month, greater than 80% of enrolled participants will undergo randomization, and six-month retention will represent greater than 80% of randomized patients.*	The outcome measures will determine whether a large-scale randomized controlled trial is feasible at our institution.
Secondary		
	Does randomization to tight blood pressure control (<135/85 mmHg on home blood pressure monitoring) following a hypertensive disorder of pregnancy result in lower mean arterial pressure (MAP) at 6 weeks and 6 months postpartum to inform the sample size for a large-scale randomized trial? *We hypothesize that among women randomized to tight blood pressure control, there will be lower mean arterial blood pressures (MAP) at 6 months postpartum and can ascertain the sample size for a large-scale randomized trial accordingly.* Does randomization to tight blood pressure control (<135/85 mmHg on home blood pressure monitoring) following a hypertensive disorder of pregnancy result in lower diastolic	Mean arterial pressure (MAP): Importantly, MAP accounts for both systolic and diastolic BP, agnd weights diastolic BP more strongly. While most hypertension trials in older adults employ systolic BP as the primary outcome, our preliminary data supports the importance of isolated diastolic hypertension in young women, particularly following a hypertensive disorder of pregnancy. Systolic blood pressure and diastolic blood pressure are surrogate values for diagnosis of elevated blood pressure at 6 weeks and 6 months postpartum.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	blood pressure, systolic blood pressure at 6 weeks and 6 months postpartum to inform the sample size for a large-scale randomized trial? *We hypothesize that among women randomized to tight blood pressure control, there will be lower systolic blood pressure, diastolic blood pressure at 6 weeks and 6 months postpartum and can ascertain the sample size for a large-scale randomized trial accordingly.*	
Tertiary/Exploratory		
	Does randomization to tight blood pressure control (<135/85 mmHg on home blood pressure monitoring) following a hypertensive disorder of pregnancy result in changes in lower care utilization through analysis of emergency room visits, hospital readmissions, and outpatient office visits for the first 6 months postpartum? *We hypothesize that among women randomized to tight blood pressure control, there will be a lower rate of postpartum care utilization.*	Postpartum care utilization comprises use of health care resources which can be ascertained by rates of emergency room visits, hospital readmissions, and outpatient office visits within our hospital system.

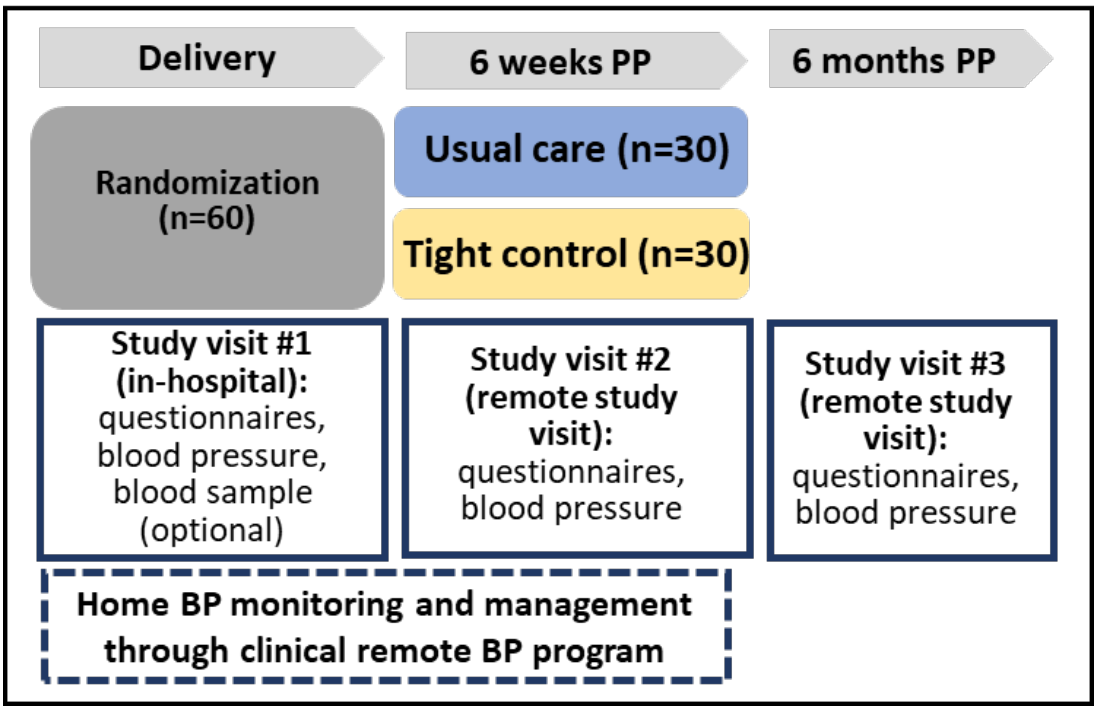
4 Study Design

4.1 Overall Design

We will determine the feasibility of conducting a randomized controlled trial of tight blood pressure control (<135/85 mmHg on home BP monitoring) vs. standard of care (<150/100 mmHg on home BP monitoring) in postpartum individuals following a HDP with assessment of individuals who are eligible, enrolled, and remain in the study until six weeks postpartum. We will further assess individuals who are retained in the study for 6 months postpartum. Lastly, we will analyze our effect outcomes to inform the sample size for a subsequent large-scale randomized trial. This will be done through analysis of mean arterial pressure (MAP), systolic

blood pressure, and diastolic blood pressure of participants at 6 weeks and at 6 months postpartum.

The study will be conducted on the postpartum unit of Magee-Womens Hospital. Participants will be enrolled at the time of postpartum hospitalization with study visit #1 occurring in the hospital. At this study visit, participants will be administered questionnaires, will provide a blood sample, and BP will be measured. Study visit #2 will be a remote study visit conducted via telemedicine or a telephone call at 6 weeks postpartum. At this visit, participants will provide questionnaires and blood pressure data. Study visit #3 will be a remote study visit conducted via telemedicine or a telephone call at 6 months postpartum. A this visit, participants will again provide questionnaires and blood pressure data. The study overview is depicted below.



4.2 Scientific Rationale for Study Design

Our central hypothesis is that conducting a single-site RCT of tighter control (<135/85 mmHg in the outpatient setting) of postpartum BP during the first six months postpartum will be feasible. Secondarily, tighter control will lead to lower blood pressure and improved cardiac remodeling. These findings will translate longer-term to a reduced risk of chronic hypertension and cardiovascular disease, an important, understudied condition in women with significant morbidity.

4.3 Justification for Dose

The current blood pressure thresholds for anti-hypertensive medication initiation for all adults as per ACC/AHA, except pregnant and postpartum individuals is 140/90 mmHg in the clinic or 135/85 mmHg at home. Accordingly, a threshold of 135/85 for home blood pressure values was selected.

4.4 End of Study Definition

The study will be concluded following assessment of blood pressure and questionnaires at study visit #3, which occurs 6 months postpartum.

5 Study Population

5.1 Inclusion Criteria

Postpartum individuals ≥18 years old with preeclampsia or gestational hypertension diagnosed by ACOG criteria and enrolled in our Connected Care remote monitoring program.

5.2 Exclusion Criteria

Fetal anomaly, pre-pregnancy hypertension, diabetes, cardiac, or chronic kidney disease.

5.3 Strategies for Recruitment and Retention

Recruitment: We will recruit 60 individuals with preeclampsia or gestational hypertension from the MWH postpartum units, using recruitment methods effectively employed by our team previously. There are approximately 100 eligible individuals per month (~1200 per year).

We plan to recruit women from the post-delivery unit with the appropriate diagnoses. Upon review of a potential subject's chart to determine eligibility, the study coordinator will flag the chart for potential eligibility. The potential participant will first be approached by the study physician or a member of the clinical care team directly caring for her to ask about her willingness to be approached for participation in a research study. If the potential participant indicated willingness to be approached, then the research team will be contacted and the potential subject will be screened regarding enrollment.

Retention: Participants will receive monetary compensation which will be distributed amongst their study visits. We propose monetary compensation of $125 total with $25 distributed at enrollment, $25 distributed at the first study visit, and $25 distributed at the second study visit and $50 at the final study visit.

Randomization and blinding: We will randomize consented participants into two arms: tight BP control (<135/85 mmHg) vs. usual care in 1:1 at the individual level. A randomization sequence using permuted block randomization with randomly varying block sizes will be generated by RedCap. This will be a pragmatic, non-masked trial. At randomization, treating physicians will be notified of their patient's participation and randomization group.

6 Study Intervention

6.1 Study Intervention(s) Administration

6.1.1 Study Intervention Description

Following hospital discharge, individuals with HDP are enrolled in a clinical home BP management program and are prompted, via a secure text message to report their BP for the first six weeks postpartum. This program is overseen by Drs. Hauspurg and Simhan. Remote monitoring nurses will be unblinded to treatment arm and will follow study protocols for enrolled participants based on study arm.

6.1.2 Dosing and Administration

Treatment group: Participants in the active arm will be initiated on oral anti-hypertensive therapy if their blood pressure is persistently elevated defined as ≥2 measures more than 4 hours apart that are greater than or equal to 135/85 mmHg with titration to maintain BP <135/85 mmHg on home blood pressure monitoring. As this is a pragmatic trial, we will not mandate the use of a specific anti-hypertensive agent, rather will leave the choice of the agent to clinical decision making.

Usual care: Usual care in this period includes initiation of oral anti-hypertensive therapy if blood pressure is persistently elevated defined as ≥2 measures more than 4 hours apart that are greater than or equal to ≥150/100 mmHg with titration to maintain BP <150/100 mmHg on home blood pressure monitoring.

6.3 Measures to Minimize Bias: Randomization and Blinding

We will randomize consented participants into two arms: tight BP control (<140/90mmHg) vs. usual care in 1:1 at the individual level. A randomization sequence using permuted block randomization with randomly varying block sizes will be generated by RedCap. We will use a permutated block randomization scheme with random block sizes in order to ensure balance within each block of participants and to preserve allocation concealment. This will be a pragmatic, non-masked trial. At randomization, treating physicians will be notified of their patient's participation and randomization group.

6.3 Study Intervention Compliance

Adherence to the study protocols through the clinical remote monitoring program will be monitored by the study team. Adherence to medication will be assessed at each study visit. Adherence to home BP monitoring will be assessed throughout the study period.

7 Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

7.2 Participant Discontinuation/Withdrawal from the Study

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized

and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if they fail to return for any scheduled visit.

The following actions will be taken if a participant fails to return to the clinic for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (at least 3 telephone calls and / or text messages)

8 Study Assessments and Procedures

8.1 Efficacy Assessments

Feasibility outcomes: As listed in Table, will include enrollment, randomization, retention.

Table. Feasibility outcomes

Feasibility outcome	Descriptive statistic	Feasibility target
Identification of participants	mean, SD, 95% CI	Review 50 medical records per month to assess for eligibility
Screening	mean, SD, 95% CI	Average screening rate of 8-10 participants/month
Enrollment	mean, SD, 95% CI	Average enrollment rate of 4-5 participants/month
Randomization	n, %, 95% CI	>80% of enrolled participants
Retention to 6 months postpartum	n, %, 95% CI	>80% of randomized participants
Study measures consistency	n, %, 95% CI	>90% of randomized participants
Acceptability	n, %, 95% CI	>80% of randomized participants based on survey questionnaires

Blood pressure measurement: Mean arterial pressure (mmHg) at six weeks and six months postpartum will be assessed at a remote research study visit. MAP is defined as the average BP during one cardiac cycle and will be calculated as MAP= SBP + 2(DBP)/ 3. BP will be measured in all women in a standardized manner by trained research staff using the same validated device as at the enrollment visit. Due to diurnal variations in BP, we will attempt to schedule all study visits between 8-10am consistent with clinical guidelines. If this cannot be performed due to participant scheduling limitations, we will ensure that BP is measured at a consistent time of the day across all visits. Following a 5-minute rest, BP will be measured in triplicate on the non-dominant arm with one-minute intervals using an appropriately sized cuff. These measures will be directly observed by research study staff.

Secondary outcomes are systolic and diastolic BP, and chronic hypertension at 1-year postpartum (stage 1 or stage 2) derived from office BP in women randomized to tight control compared to women to receiving usual care. We will also compare the use of anti-hypertensive agents across the study period, quantitatively assessed using the therapeutic intensity score [TIS], which is a summary measure that accounts for the number of medications and the relative doses received, which will be summarized across the study period and compared by randomization arm. As an exploratory analysis, we will quantitatively simulate BP based on confounding effects of anti-hypertensive medications using published metrics of the lowering effect of various anti-hypertensive agents. Finally, we will evaluate care utilization across study arms, including postpartum readmission and Emergency Room visits

Questionnaires: The participant will complete questionnaires about demographics, medical history, obstetric and gynecologic history, physical activity, mood, diet, breastfeeding, sleep, and overall health and support. At subsequent visits, the participant will also answer questions about the intervention.

8.2 Safety and Other Assessments

Answering Questionnaires: There is a possibility of emotional discomfort associated with answering the questionnaire as some of the questions may be considered "personal" and answering them might be stressful or embarrassing. Participants may skip questions for which they feel uncomfortable.

Risks of the Tight Control Intervention Program: For some women, there may be a small but present risk of hypotension, meaning your blood pressure goes too low. If this occurs, it may cause symptoms such as dizziness, shortness of breath, palpitations, light-headedness, and/or falls. We advise women who are experiencing these symptoms to immediately contact their health-care provider and to avoid carrying their newborn due to risk of falls. Additionally, we will monitor rates of breastfeeding continuation given the theoretical risk for decreased milk supply.

9 Statistical Considerations

9.1 Statistical Hypotheses

- We hypothesize that randomizing individuals to tight vs. less tight BP control in the postpartum period will be feasible and will lead to improved BP longer-term.

9.2 Sample Size Determination

We will focus on the 60 randomized participants. While the sample size may appear to be limited, the goal of the pilot is to collect information for planning a larger efficacy study. Our sample size is based on the confidence interval for our feasibility measures as outlined above. Assuming 30 participants within each study group and a 5% type I error rate, we will have the ability to estimate within-arm 95% confidence interval margin-of-errors of no more than 0.18 for each of our feasibility outcomes. For our efficacy outcomes, in our prior work, mean MAP at 6 weeks postpartum following a HDP was 94 (SD 8) mmHg. Although the primary objective of this pilot trial is obtaining information on feasibility and acceptability used to inform design of a confirmatory trial, we will perform a preliminary test for efficacy to confirm that this line of research warrants further study. Assuming a study retention of 80% (n=48 individuals, which we exceeded in our pilot work) and a 20% type I error rate, we will have 80% power to detect a difference of 5 mmHg in mean MAP at visit 2. Because this is a pilot study designed to test feasibility outcomes, we are using a higher than 5% type 1 error rate for the efficacy analysis because any "positive" finding in our pilot will be followed by a confirmatory efficacy trial.

9.3 Populations for Analyses

All analyses will be performed using the intention-to-treat principle.

9.4 Statistical Analyses

9.4.1 General Approach

Baseline characteristics, such as race/ethnicity, age, parity, and insurance, will be reported to assess representativeness of the source population. Descriptive summaries will include the mean and standard deviations (or medians and quartiles for skewed distributions) for continuous variables and frequencies and proportions for categorical variables. We will calculate 95% CI for means and proportions and will construct boxplots and histograms to visually examine the distributions of continuous variables. Due to the pilot nature of this RCT, hypothesis testing is not the primary focus, but rather estimation within each study group. We will calculate estimates and 95% CI for the feasibility and efficacy outcomes overall and by study group.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

Our primary feasibility outcomes will be the number (proportion) of women who are eligible, screened, enrolled, and remain in the study at each outcome assessment. To ensure adequate retention of postpartum women, we will identify any issues related to recruitment, enrollment, and retention that will be necessary to account for, when determining the sample size estimated for the future trial. Reasons for exclusion and participant refusal will be tracked at the time of screening. We will assess reasons for participant attrition at the time of withdrawal. We will determine the proportion of women who remain on the treatment assigned at the beginning of the pilot. We will assess adherence as outlined above. Acceptability will be assessed through semi-structured and open-ended evaluation questions, which will assess satisfaction, perceived

benefits/harms, evaluation of interventions and BP monitoring and medication monitoring protocols using standard questionnaires.

9.4.3 Analysis of the Secondary Endpoint(s)

The primary comparison of interest is between the tight control (n=30) and usual care (n=30) groups to explore whether there is any beneficial effect of tight BP control on mean visit MAP at 6 weeks and 6 months. Additionally, we will examine the effect of the intervention on mean systolic and diastolic blood pressure. As an exploratory measure, we will use generalized linear models to compare outcomes between study arms as well as assess potential mediation with relevant co-variates. As an exploratory analysis, we will also use mathematical models to quantitatively simulate BP given the confounding effect of anti-hypertensive agents based on published treatment effects.

9.4.4 Safety Analyses

9.4.5 Baseline Descriptive Statistics

Baseline descriptive statistics will be compared between groups. Continuous variables will be compared using Student t-test or Wilcox-rank sum as appropriate. Categorical variables will be compared using chi-squared or Fisher's exact tests as appropriate. If any differences are noted between groups in baseline characteristics, they will be included in multivariable models. In multivariable analysis, the ANCOVA model will be used for continuous variables and a logistic regression analysis for categorical variables. We will include age and self-reported race as covariates.

9.4.6 Planned Interim Analyses

No interim analyses are planned.