Title: Lasix for the Prevention of De Novo Postpartum Hypertension: A Randomized Control Trial (LAPP Trial)

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1. Proposal abstract

1.1 Scientific abstract

The overarching goals of our study are to (i) assess whether postpartum administration of a loop-diuretic reduces blood pressure prior to discharge in women at high risk for de novo postpartum hypertension; (ii) evaluate whether this reduction in blood pressure reduces the need for initiation of therapies to treat severe de novo postpartum hypertension; and (iii) evaluate whether this reduces the risk of hypertension-associated morbidity in the postpartum period.

Hypertensive disorders of pregnancy are one of the leading causes of maternal morbidity and mortality worldwide.[1,2] The majority of clinical research has focused on pregnancy-related hypertension that develops in the antenatal period, while studies of the incidence, risk factors, and prevention of postpartum hypertension are limited. In particular, there is a paucity of data about the clinical entity known as de novo postpartum hypertension, in which women who are normotensive throughout pregnancy and delivery subsequently go on to develop high blood pressure in the immediate to late postpartum period. Of those with postpartum preeclampsia, 33-69% were normotensive antepartum. [3-7]

Early identification and treatment of antepartum preeclampsia has been shown to decrease some severe maternal outcomes. Conversely, women with de novo postpartum hypertensive disorders remain among the highest risk for severe maternal morbidity due to decreased surveillance and lack of data regarding identifiable and modifiable risk factors to facilitate stratification of monitoring, preventive therapies and intervention.[8] Of women admitted with postpartum hypertensive complications, for example, two retrospective series estimate rates of eclampsia up to 78% in women with no antenatal diagnosis of hypertensive disorders of pregnancy, compared to rates ranging from 4.6% to 13.6% in women with antepartum or intrapartum diagnoses of hypertensive disorders.[3,9]

Over the past two decades, multiple randomized controlled trials have demonstrated a benefit in the use of oral loop-diuretics in decreasing postpartum systolic blood pressure, promoting faster normalization of blood pressure and decreasing the need for antihypertensive therapy in women with an antenatal diagnosis of preeclampsia.[10-12] Given the implication of the normal physiologic auto-infusion of sequestered extravascular fluid into the intravascular space in the pathogenesis of hypertensive disorders in the postpartum period, we propose that this same therapy may have benefits in reducing hypertensive episodes and need for therapy in other women at high risk for postpartum hypertensive complications – specifically de novo postpartum

hypertension. In a randomized placebo-controlled trial design, we propose to use an oral loop diuretic (i.e. furosemide) to evaluate whether we can help prevent de novo postpartum hypertension by reducing blood pressure after delivery in high-risk women. We hypothesize that postpartum administration of the loop diuretic furosemide in women at high risk of developing de novo postpartum hypertension will reduce blood pressure at the time of discharge compared to placebo. The primary outcome of arterial blood pressure (MAP) will be compared between the study groups using student's t-test. Ultimately, we hypothesize that this will reduce the need for therapies to treat severe postpartum hypertension and will reduce hypertension-associated morbidity in the postpartum period. For analysis of categorical data in independent samples, the Chi-squared test or Fisher exact probability test will be utilized. Continuous data that satisfy the assumptions of normality and homoscedasticity (homogeneity of variance) will be analyzed by t-test.

1.2 Lay abstract

New-onset high blood pressure related to pregnancy is one of the leading causes of maternal complications and death worldwide.[1,2] Most of what is known about pregnancy-related high blood pressure comes from studies of women who develop high blood pressure while they are still pregnant. There is little data that exists about the clinical entity known as "de novo postpartum hypertension", in which women who have normal blood pressure throughout pregnancy and delivery subsequently go on to develop high blood pressure within two days to six weeks after giving birth, also known as the postpartum period. Of all the women who develop high blood pressure in the postpartum period, one third to two thirds of them had normal blood pressure during pregnancy.[3-7]

Early identification and treatment of the complications of pregnancy-related high blood pressure while women are still pregnant have been shown to decrease some severe maternal outcomes, such as seizures (i.e. eclampsia), strokes, and death. On the other hand, women with de novo postpartum hypertension remain among the highest risk for severe maternal complications, such as eclampsia.[8] This occurs because there is a lack of data to identify who is at high risk for de novo postpartum hypertension and may need continued close follow up after delivery and what preventive measures or treatments can be provided to reduce the risk of complications. Studies of women admitted to the hospital after delivery for high blood pressure-related complications estimate that the rates of eclampsia were as high as 78% in women who had normal blood pressure during pregnancy compared to rates ranging from 4.6% to 13.6% in women with were diagnosed with high blood pressure during pregnancy or labor and delivery.

Over the past two decades, high quality data has shown that for women diagnosed with preeclampsia during pregnancy, giving them a medication known as a loop diuretic after they deliver reduces their blood pressure, helps their blood pressure to return to normal faster, and reduces their need for high blood pressure medication.[10-12] This same therapy may have similar benefits in women at high risk for new-onset high blood pressure after they give birth, and may ultimately reduce their risk of severe complications, such as seizures and strokes.

2. Proposal body

2.1 Background

Hypertensive disorders of pregnancy are one of the leading causes of maternal morbidity and mortality worldwide.[1,2] The majority of clinical research has focused on pregnancy-related hypertension that develops in the antenatal period, while studies of the incidence, risk factors, and prevention of postpartum hypertension are limited. In particular, there is a paucity of data about the clinical entity known as de novo postpartum hypertension, in which women who are normotensive throughout pregnancy and delivery subsequently go on to develop high blood pressure in the immediate to late postpartum period. Of those with postpartum preeclampsia, 33-69% were normotensive antepartum. [3-7]

Early identification and treatment of antepartum preeclampsia has been shown to decrease some severe maternal outcomes. Conversely, women with de novo postpartum hypertensive disorders remain among the highest risk for severe maternal morbidity due to decreased surveillance and lack of data regarding identifiable and modifiable risk factors to facilitate stratification of monitoring, preventive therapies and intervention.[8] Of women admitted with postpartum hypertensive complications, for example, two retrospective series estimate rates of eclampsia up to 78% in women with no antenatal diagnosis of hypertensive disorders of pregnancy, compared to rates ranging from 4.6% to 13.6% in women with antepartum or intrapartum diagnoses of hypertensive disorders.[3,9]

Over the past two decades, multiple randomized controlled trials have demonstrated a benefit in the use of oral loop-diuretics in decreasing postpartum systolic blood pressure, promoting faster normalization of blood pressure and decreasing the need for antihypertensive therapy in women with an antenatal diagnosis of preeclampsia.[10-12] The rationale for its efficacy is the implication of the normal physiologic auto-infusion of sequestered extravascular fluid into the intravascular space in the pathogenesis of hypertensive disorders in the postpartum period. Given that this same mechanism may play a role in the pathogenesis of postpartum hypertension, **we propose that this same therapy may have benefits in reducing hypertensive episodes and need for therapy in other women at high risk for postpartum hypertensive complications – specifically de novo postpartum hypertension. Therefore, the purpose of this study is to evaluate whether furosemide can help prevent de novo postpartum hypertension by reducing blood pressure after delivery in high-risk women.**

2.2 Specific aims

Our objective is to trial furosemide in women at high risk for developing de novo postpartum hypertension in a randomized control design, with an aim to reduce blood pressure at the time of discharge from the delivery hospitalization and thereby reduce the frequency of postpartum hypertensive episodes requiring therapy and reduce severe morbidity and mortality.

Specific Aim 1. To compare the mean blood pressures over the 24 hours prior to discharge or prior to antihypertensive therapy initiation (whichever occurs first) in women who have been randomized to a 5-day course of PO furosemide 20 mg daily (study drug) to those who have been randomized to a 5-day course of PO placebo daily (placebo). We hypothesize that women taking PO furosemide 20 mg daily will have lower mean blood pressure in the 24 hours

prior to discharge or prior to antihypertensive therapy initiation compared with patients taking placebo.

- **Sub-aim 1: To compare the rates of diagnosis of postpartum hypertension and preeclampsia between those who have been randomized to the study drug and those randomized to placebo from the time of delivery to 6 weeks postpartum.** We hypothesize that women randomized to the study drug will have lower rates of postpartum hypertension and preeclampsia.
- **Sub-aim 2: To compare percentage of elevated blood pressures postpartum between those who have been randomized to the study drug to those randomized to placebo from the time of delivery to 6 weeks postpartum.** We hypothesize that women randomized to the study drug will have fewer hypertensive episodes.
- **Sub-aim 3: To compare the frequency of postpartum hypertension-related triage and emergency department visits between those who have been randomized to the study drug to those randomized to placebo from the time of discharge to 6 weeks postpartum.** We hypothesize that women randomized to the study drug will have fewer triage and emergency department visits for hypertension-related complaints episodes after discharge.
- **Sub-aim 4: To analyze factors associated with response to therapy.** We hypothesize that factors such as degree of lower extremity edema and indication for high risk status will be associated with greater response to therapy.

Specific Aim 2. To compare rates of initiation of hypertensive therapies in women randomized to the study drug compared to those randomized to placebo. We hypothesize that women randomized to the study drug will be less likely to be initiated on hypertensive therapies between delivery and 6 weeks postpartum.

Specific Aim 3. To compare rates of severe maternal morbidity in women randomized to the study drug compared to those randomized to placebo from the time of discharge to 6 weeks postpartum. We hypothesize that women randomized to the study drug will have lower rates of severe maternal morbidity between delivery and 6 weeks postpartum compared to those randomized to placebo.

- **Sub-aim 1: To compare hypertensive-related unscheduled presentations between those who have been randomized to the study drug and those randomized to placebo.** We hypothesize that women randomized to the study drug will have fewer triage and emergency department visits for hypertension-related complaints episodes after discharge.
- **Sub-aim 2: To assess adverse effects of therapy in the study group and the control group.** We hypothesize that there will be no difference in adverse effects, such as discontinuation of breastfeeding, hypotension, and electrolyte abnormalities in women randomized to the study drug compared to those randomized to placebo.
- **Sub-aim 3: To analyze factors associated with incidence of severe maternal morbidity in the study group and the control group.** We hypothesize that factors such as racial and ethnic identity and age will be associated with increased incidence of severe maternal morbidity.

2.3 Methods

2.3.1 Study Design

This will be a randomized control trial, in which women who are at high risk of developing de novo postpartum hypertension will be assigned to either a five-day course of PO furosemide 20 mg daily or a five-day course of PO placebo after delivery.

Patients will be informed of the study in the antenatal period, within four weeks of their estimated date of delivery or on admission to labor and delivery and will be deemed eligible, enrolled and randomized from the postpartum service within 8 hours after delivery. Randomization will be performed by the Columbia Research Pharmacy, and the study drug or placebo will be dispensed to the postpartum floor to be administered by the patient's assigned postpartum nurse. Blood pressure measurements will occur every six hours (or more if clinically indicated) until the time of discharge. Upon discharge, the remainder of the five-day course of the study drug or placebo will be dispensed to the patient to complete. Patients in both groups will be asked to check their blood pressure twice per day, once in the morning and once in the evening, and will receive text message reminders twice a week. In order to check their blood pressures after discharge, patients in both groups will be given a Philips Bluetooth-enabled blood pressure cuff, which will transmit blood pressure measurements via Bluetooth from the monitor to the eCC. These patients will be educated on the use of and enrolled in the software by research investigators who have been in-serviced on the devices prior to discharge. The tablets are cellular-enabled, so no wireless connection is needed in the patient's home. Criteria for contacting their provider will be reviewed with and provided in writing to the patients upon discharged. No changes will be made to standard hypertensive treatment protocols for either group.

Patients in both groups will be given an appointment to follow-up with their obstetric provider in the office at approximately 14 days postpartum and at about 6 weeks postpartum. The number of measurements *total* and the number of measurements that were *elevated* will be ascertained for each group at this visit.

Patients in both groups will also be prompted to answer two electronic surveys (attached as a separate document to this IRB application) regarding symptoms of preeclampsia, symptoms of volume overload, and breastfeeding continuation at about two weeks postpartum and at the conclusion of the study period. A text message reminder will be sent to patients at the time that each survey is due. A research coordinator will call to obtain responses to the survey questions if patients are unable to complete the survey electronically.

Patients in both groups will be followed from recruitment until six weeks postpartum.

2.3.2 Inclusion Criteria

Women who meet the following criteria will be eligible for the study:

1) Postpartum women
2) No antenatal diagnosis of hypertensive disorder of pregnancy at the time of admission for delivery, defined as existing chronic hypertension diagnosis or documented blood pressure of ≥140 systolic OR ≥90 diastolic on at least 2 occasions at least 4 hours apart

prior to delivery admission who do not go on to get magnesium for seizure prophylaxis by the time of delivery

3) At least 18 years of age
4) English or Spanish speakers
5) One or more of the following high risk factors and/or two or more moderate risk factors for development of de novo postpartum hypertension:
    a. High risk
        i. Pregestational diabetes mellitus
        ii. Renal disease
        iii. Autoimmune disease (systemic lupus erythematosus, antiphospholipid syndrome)
        iv. Multifetal gestation
        v. Gestational diabetes mellitus, A2 (i.e. medication-dependent)
        vi. History of preeclampsia in a prior pregnancy (not including the index pregnancy)
    b. Moderate risk
        i. Primiparity
        ii. Obesity (BMI $\geq$ 35 kg/m^2)
        iii. Age $\geq$ 35 years
        iv. Black or African-American race
        v. Family history of preeclampsia

2.3.3 Exclusion Criteria

1) Non-English and Non-Spanish speakers
    - The consent form will only be available in these 2 languages
2) Women with a contraindication to diuretic therapy
3) Women who have used diuretics in the two weeks prior to delivery

2.3.4 Recruitment, Screening and Enrollment

Recruitment and Screening

A study team member will perform daily chart screen of all women at least 36 weeks of gestation who are presenting for prenatal visit with a CUIMC provider and of all women admitted to the CUIMC labor and delivery unit (CHONY 10 Tower) for delivery. Permission from healthcare providers will be obtained prior to the OB study team member contacting participants. Women will be approached at the aforementioned times to be informed of the study and of their conditional eligibility. Final eligibility will be determined on admission to labor and delivery and eligible women will then be recruited on the postpartum units (CHONY 5 central, 6 central and 10 central).

We will abide by the CUMC policy that researchers cannot directly approach a patient for recruitment until that patient has been informed of the study by a provider who has ascertained that the patient is willing to discuss the study with the investigators. This will be documented in the research record.

We will also ensure that if patients are laboring, they are competent to consent to research and haven't received systemic opioids or sedative medications within the past 2 hours. We will also ensure the cooperation of the labor room nurse, obstetric care provider, and patient support persons in the discussion of proposed research and study informed consent process. Whenever practical and feasible, information about research on Labor and Delivery will be made available to patients prior to onset of painful labor and/or after placement of epidural analgesia, if such analgesia is desired by the patient.

Informed Consent Process

Research coordinators and study physicians listed on this protocol may obtain informed consent. Study personnel will consent participants in person, face-to-face, when they receive notification by a provider of an eligible patient. Participants will be consented in English or Spanish by personnel fluent in that language or with the use of NYP translators and a full consent in their language. Recruitment will occur in a private setting, in a non-coercive manner, with ample time to ask questions and receive satisfactory answers.

Patient written informed consent and HIPAA authorization to participate in the study will be collected on an iPad or laptop. In-person electronic signature will be captured on the electronic informed consent form. Study personnel obtaining consent will be physically present at time of signature. A paper copy of the signed informed consent form will be given to the patient. A copy of the signed consent form will also be placed in the patient's inpatient paper chart. The time of consent will be documented on the consent form and in the medical record.

Consent forms will be available in both English and Spanish to accommodate our expected population. A witness will be required for our non-English speaking patients.

At the time of the consent, the Informed Consent Process will begin with a concise and focused presentation of the key information about the research study. The collaborating investigators will explain the study, and potential subjects will have an opportunity to discuss the information provided. The collaborating investigators will answer any questions. The Informed Consent Process as a whole presents information in sufficient detail relating to the research study. Consent will be obtained to measure blood pressures postpartum. Consent will be obtained to review medical records to abstract pertinent sociodemographic and clinical information and to call patients to obtain the aforementioned information if not able to be abstracted from the medical record. Consent will be obtained to administer electronic surveys and collect home blood pressure measurements at two postpartum study visits. Patients still meeting inclusion criteria will be randomized at within eight hours of delivery on the postpartum service.

Enrollment

After obtaining written informed consent, participants will be randomized to either the study drug, as defined above, or placebo. Randomization will occur through the Columbia Research Pharmacy in REDCap. The medication intervention will be dispensed to the patient's postpartum unit and administered by the nursing staff once daily beginning within eight hours of delivery. The patient, the patient's nurse, and the patient's inpatient obstetric provider will not be informed

of the patient's randomization group, to avoid potential biases stemming from differences in inpatient care. Participants will be enrolled in the study from the time of randomization until 6 weeks postpartum.

2.3.5 Equipment and Software

All study participants will receive a Philips Home Telehealth Solution kit, complimentary of participating in the study, which includes several FDA/FCC approved devices. NewYork-Presbyterian has a contract in place with Philips (attached separately to this IRB application under "Philips Contract 5.10.21") which allows the hospital to utilize Philips telehealth programs for its patients. **The investigators had no role in the signing of this contract and have no financial interests in this program.** The following equipment is included in the Philips kit:

Device	US 510(k)
A&D Blood Pressure Meter, regular or small cuff version UA-767PBT-Ci	Class II K043217 FCC:POOWML-C40
eCareCoordinator (eCC) Suite	K171029
Samsung Galaxy Tab E 8.0" model SM-T377A	Not a medical device, no associated 510(k) FCC: A3LSMT377A

The instructions that patients will receive for use of the tablet and the blood pressure meter are attached separately to this IRB application ("Philips A&D Cuff Instructions").

At the conclusion of the 6-week study period (in other words, after the scheduled postpartum visit or the time when that visit was supposed to occur, if the patient did not present), the patient will be expected to return the kit. The full patient terms of use are attached to this IRB application as a separate document ("Philips Patient Terms of Use").

2.3.6 Outcomes

1) **Primary outcome:** Our primary outcome will be the difference in mean arterial pressure (MAP) averaged over the 24 hours prior to discharge or the 24 hours prior to antihypertensive therapy initiation (whichever occurs first).
2) **Secondary outcomes:** Secondary outcomes will include:
    1. Rates of de novo postpartum preeclampsia – determined at discharge, at 2 and at 6 weeks postpartum
    2. Percentage of recorded blood pressure that are elevated (>140 systolic OR >90 diastolic) – calculated at the time of discharge, at 2 weeks, and at 6 weeks

3. Rates of magnesium sulfate administration – determined at discharge, at 2 and at 6 weeks postpartum
4. Time to discharge
5. Rates of initiation of antihypertensives – determined at discharge, at 2 and at 6 weeks postpartum
6. Rates of severe maternal morbidity (e.g. stroke, seizure, PRES) – determined at 6 weeks postpartum
7. Mean frequency of triage or ED presentation/readmission – determined at 2 and at 6 weeks postpartum
8. Breastfeeding continuation rates – determined at about 2 weeks and at 6 weeks postpartum
9. Neonatal outcomes

2.3.7 Measures

The following data will be collected for analysis.

1) **To be collected on enrollment/prior to hospital discharge:**
    1. **Demographic and social factors.** Date of birth, self-reported race/ethnicity, cultural background [place of birth (US or not), years living in the US, and primary language spoken in the home], marital status, highest level of maternal education attained, employment status, household income, and insurance status will be elicited from the patients on enrollment
    2. **Pregnancy history.** On enrollment, participants will be asked about the number and outcomes of prior pregnancies
    3. **Prenatal care history.** Location of prenatal care, gestational age on initiation of prenatal care and number of prenatal visits will be extracted from the EHR when possible and verified by the participant on enrollment.
    4. **Delivery history.** Mode of delivery and baby's disposition will be collected on enrollment
    5. **Medical history**. Other medical history will be extracted from the EHR and verified by the participant on enrollment
    6. **Health behaviors.** Current and prior smoking, alcohol, and illicit drug use will be elicited on enrollment.
    7. **Weight and height.** Height, pre-pregnancy weight, first documented weight during the pregnancy, and weight at enrollment, will be obtained on enrollment and extracted from the EHR. Body mass index (BMI) will be calculated as height (cm)/weight (kg)2.
    8. **Hospital length of stay.** defined as days AFTER delivery that the patient is admitted to the hospital; this will be ascertained upon hospital discharge
    9. **Medications.** discharge antihypertensive medications will be collected upon discharge
2) **To be collected throughout the study period:**
    1. **Blood pressures.** Blood pressure recordings on the postpartum unit will be abstracted from the chart. Mean arterial pressure will be calculated for each blood pressure measured within the 24 hours prior to discharge or prior to

antihypertensive therapy initiation (whichever comes first) and will be averaged over that time period. Participants will be asked to provide a record of the blood pressures they are recording at home, and the blood pressures from their office visits will be recorded as well. Percentage of scheduled blood pressure readings that are recorded will be compared between groups. Incidence of elevated blood pressures during this time will also be compared between groups.

2. **Adherence.** For both groups, proportion of medication course completed will be recorded
3. **Time to initiation of medications.** For both groups, time to initiation of anti-hypertensive medications will be tracked
4. **Final plan at 6 weeks.** For both groups, continuing medication regimens at 6 weeks will be collected.
5. **Hospital readmissions.** Hospital readmission for any indication will be collected for both groups
6. **Triage/ED visits.** Presentation to the obstetric triage unit or the emergency department for any indication will be collected for both groups
7. **Maternal morbidity and mortality.** Incidences of eclampsia, stroke, PRES, maternal death will be collected for both groups
8. **Breastfeeding continuation.** Rates of breastfeeding continuation will be collected for both groups
9. **Adverse effects.** Incidences of hypotension, electrolyte abnormalities, and development of renal insufficiency will be collected for both groups.

2.3.8 Definitions

Chronic hypertension will be defined according to ACOG guidelines as blood pressure measurement of EITHER ≥140 mm Hg OR diastolic ≥90 mm Hg on at least 2 occasions, at least 4 hours apart, prior to 20 weeks gestation.[2]

Hypertensive disorders of pregnancy will be defined according to ACOG guidelines.[2] The minimum criteria for a diagnosis of HDP are as follows:

- Blood pressure measurement of EITHER systolic ≥140 mm Hg OR diastolic ≥90 mm Hg on at least 2 occasions, at least 4 hours apart, between 20 weeks gestation and delivery
- Blood pressure measurement of EITHER systolic ≥160 mm Hg OR diastolic ≥110 mm Hg on at least 2 occasions qualifies as severe features

Diagnosis of hypertensive disorder of pregnancy will be determined at the time of admission for delivery.

The following investigations are routinely undertaken in the clinical setting once HDP is identified in order to further categorize HDP into more specific diagnoses. These results will be reviewed for each patient to ensure the correct diagnosis has been assigned to the patient. Blood pressure findings as above with none of the findings listed in the table below satisfies a diagnosis of gestational hypertension.

Type of test	Cutoffs	Diagnosis

Urine	-24-hour protein concentration > 300 mg OR -Protein/Creatinine ratio > 0.3	Preeclampsia
Serum	-Platelets <100,000/microliter OR -Creatinine >1.1 mg/dL, or doubling from baseline OR -LFTs > twice the upper limit of normal concentration or twice baseline	Preeclampsia with severe features
Signs/symptoms: any of the following, if not accounted for by another diagnosis	-New-onset, refractory cerebral or visual disturbances -Severe persistent right upper quadrant or epigastric pain unresponsive to medication -Pulmonary edema -Blood pressure ≥ 160 systolic OR ≥110 diastolic	Preeclampsia with severe features
Serum	-Platelets <100,000/microliter AND -Evidence of hemolysis AND -LFTs > twice the upper limit of normal concentration or twice baseline	Hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome
Signs/symptoms	New-onset, grand mal seizure, with no history of seizure disorder and not accounted for by any other diagnosis	Eclampsia

De novo postpartum hypertensive disorders of pregnancy will be defined according to the aforementioned criteria and definitions, except for their timing of occurrence after delivery, and in the absence of any antenatal diagnosis of a hypertensive disorder of pregnancy.

2.4 Statistical Analyses

2.4.1 Sample size and statistical power

A case-control study of women who were normotensive at delivery but who were later hospitalized with a diagnosis of severe preeclampsia compared to women who remained normotensive in the postpartum period and women who were diagnosed with preeclampsia in the antenatal period determined that differences in mean arterial blood pressure could be detected following delivery. This retrospective review determined that women who developed de novo postpartum preeclampsia had a greater increase in MAP after delivery than normotensive women (5.0 ± 6.4 mm Hg vs 0.2 ± 6.0 mm Hg, $p < 0.004$). [13] Though data is scarce on whether a change in MAP can be detected in women with a broader diagnosis of de novo postpartum hypertension, using this reference data to assign an effect size of 5 mm Hg with standard deviation of 6.4 mm Hg and a baseline MAP of 83 mm Hg will provide a conservative estimate of a clinically meaningful change. For a power of 90%, a significance level 5%, and anticipated post-randomization losses of 10%, 41 patients will be needed for each group, or 82 patients total.

2.4.2 Statistical analysis

For analysis of discrete (categorical) data in independent samples, the Chi-squared test or Fisher exact probability test will be utilized. For group comparisons, continuous data that satisfy the assumptions of normality and homoscedasticity (homogeneity of variance) will be analyzed by t-test (for 2 independent samples) or analysis of variance (>2 groups, ANOVA) with post hoc comparisons by Scheffe tests. When possible, continuous data that do not fulfill the aforementioned assumptions will be mathematically transformed (e.g., logarithmic transformation) before performing t-tests or ANOVA. In some cases, data that do not satisfy these assumptions will be analyzed by nonparametric methods [Mann-Whitney U Test (for two independent samples) or Kruskal-Wallis One-Way ANOVA (for more than two independent samples)]. Significant Kruskal-Wallis ANOVAs will be followed by Dunn tests for post hoc analysis. The degree of linear association between variables will be measured by the Pearson product moment correlation coefficient or the Spearman rank-order correlation coefficient and their corresponding tests of significance. Multivariate linear or logistic regression will be utilized where appropriate. In all cases, statistical significance will be assumed when $p<0.05$. Propensity score analysis will be used as a balancing score as deemed necessary.

2.4.3 Strengths and limitations

Strengths of our study include a randomized control design, as well as a large cohort of patients who will be eligible for enrollment. CUIMC has 9 obstetric clinics which annually experience 27,612 deliveries, of which only 2,853 would be excluded based on an antenatal diagnosis of HDP.

Project limitations include potential fear among patients of a medication that is not standardly used in postpartum management that could limit enrollment. Additionally, patients are being discharged earlier than prior to the start of the COVID-19 pandemic, which would limit the amount of blood pressure data that can be collected and may limit the amount of time necessary to be able to see the effect of the diuresis; however, extended follow up and secondary outcomes included in the analysis, particularly review of logs at 10-14 days postpartum may assist in capturing the effect of the intervention after discharge.

2.5. Anticipated outcomes

The primary outcome will be the difference in the mean arterial blood pressure in the 24 hours prior to discharge or antihypertensive therapy initiation (whichever occurs first) between patients in the study drug group and those in the placebo group. We anticipate that the patients randomized to the study drug will have a significantly lower mean arterial blood pressures than those randomized to placebo. We propose that this will lead to faster normalization of blood pressures, reduce the rate of development of de novo hypertension, specifically preeclampsia, and reduce the morbidity and mortality associated with de novo postpartum hypertension without adverse effect.

2.6 Significance

There are several knowledge gaps in the postpartum management of women with pregnancy-related hypertension. Specifically, no management recommendations or interventions for women at risk for developing de novo postpartum hypertension have been described, despite the evidence for their high risk of morbidity. These knowledge gaps have important clinical implications and answering them will provide valuable information regarding the low-cost interventions to reduce morbidity. The overall goal of this project is to collect empiric data for future guidelines on the use of diuretic therapy among postpartum women at risk for de novo postpartum hypertension.

2.7 Timeline

Enrollment is planned to begin in July of 2021, as soon as IRB approval is granted. The sample size required is 41 patients per group for a total of 82 patients. We anticipate that these patients will be successfully recruited into the study within a 12-month period, ending approximately in July of 2022. These patients will need to be followed until 6 weeks postpartum. We anticipate that the study will be completed by August 2022.

2.8 Environment

The Columbia Department of OB/GYN brings substantial experience and skill in organizing and participating in clinical research. We have a strong track record in all areas of collaborative research including protocol design, implementation, data analysis and dissemination of findings. Our productivity is facilitated by a number of factors: (1) A critical mass of academic full time faculty with sufficient time and skill to perform clinical research, (2) the presence of a diverse patient population willing to participate in research initiatives, and (3) an established research environment in which clinicians accept participation in research initiatives as a major role of a teaching institution. This has led to a longstanding reputation for excellence in clinical research.

Of utmost importance is our research infrastructure with a proven record of success, which is embedded in the elaborate system of prenatal clinics and obstetric services and complemented by our large and diverse population of over 6,600 deliveries per year, advanced support systems,

strong division of Neonatology, outstanding follow-up programs and a patient population proven to be receptive to participation in research. The research staff is trained and certified in Good Clinical Practice, HIPPA, Blood Borne Pathogen Handling, and IATA Shipping Regulations. All staff is capable of collecting patient samples, cord blood and placental processing (including RNA, proteomics and DNA). Our research staff of over 25 individuals are trained and certified in each ongoing project. This maximizes efficiencies in recruitment and the performance of study procedures and also allows staff to share the responsibility of on-call coverage.

The Department of OB/GYN maintains a centralized administrative research office that manages pre- and post-award grant administration, and oversees roughly $10 million in sponsored research funding annually. The Office analyzes, monitors, and evaluates the Department's research activities including all federal and non-federal sponsored awards and contracts. They ensure the efficient, cost-effective administration and financial management and ensure compliance with internal and external policies and procedures.

2.9 Investigators

We are uniquely qualified to perform this project, as we are in a large medical center, with a diverse patient population. Our research study will take place at Columbia University, a large academic center actively involved in a myriad of academic studies. The co-principal investigators, Dr. Cynthia Gyamfi-Bannerman and Dr. Russell S. Miller, completed their fellowship in Maternal-Fetal Medicine. Dr. Gyamfi-Bannerman is the Chair of Obstetrics, Gynecology, and Reproductive Sciences at University of California San Diego. Prior to that, she served as the Columbia Center PI for the Maternal-Fetal Medicine Unit Network, overseeing multiple randomized controlled trials. Dr. Miller is the Sloane Hospital for Women Associate Professor of Prenatal Pediatrics (in Obstetrics and Gynecology) and Medical Director of the Carmen and John Thain Center for Prenatal Pediatrics at Columbia University. Additionally, he has overseen multiple clinical trials. He is also the Director of the Maternal-Fetal Medicine fellowship program at Columbia University and a dedicated teacher and mentor in the residency program, as well. Dr. Ukachi Emeruwa, a fellow in Maternal-Fetal Medicine, has professional interests geared toward system-based program implementation, as well as behavioral health interventions centered around improvements in maternal health. Her research has begun to focus on investigations of clinical evidence that will inform systems-based practices for improvement of outcomes related to high-risk obstetrical issues, such as hypertensive disorders of pregnancy in particular.

Support for database construction and management will primarily come from Cynthia Masson, Director of Clinical Information System Design and Innovation and head of the Columbia University's Department of Obstetrics and Gynecology Interdepartmental CORE Data Team. She has assisted multiple single and multi-center funded and unfunded studies in obtaining and capturing research, clinical and operational data and providing a stream-lined process for building complex databases and translating complex data for seamless data analysis.

As part of a major academic research center, we additionally have the continued support of medical students, residents and experienced research assistants.

2.10 Risks, Benefits, and Monitoring

2.10.1 Risks

Lasix (furosemide) is in a class of drugs call diuretics and is commonly used to treat edema (swelling) and hypertension. Lasix is considered safe for use in adults and pediatric patients. If given in excessive amounts, Lasix can cause dehydration and electrolyte imbalances. Other possible side effects include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, arrhythmia, or gastrointestinal disturbances such as nausea and vomiting. Increases in blood glucose and alterations in glucose tolerance tests (with abnormalities of the fasting and 2-hour postprandial sugar) have been observed, and rarely, precipitation of diabetes mellitus has been reported.

In patients with severe symptoms of urinary retention (because of bladder emptying disorders, prostatic hyperplasia, urethral narrowing), the administration of furosemide can cause acute urinary retention related to increased production and retention of urine. Thus, these patients require careful monitoring, especially during the initial stages of treatment.

Lasix is contraindicated in patients with anuria and in patients with a history of hypersensitivity to furosemide. Therefore, if you do not produce urine or if you have ever had an allergic reaction to furosemide, you will not be able to participate in the study.

A very small amount of Lasix may pass to the baby through breast milk. Lasix may also inhibit lactation.

Since the use of the study drug is investigational, there may be other risks that are unknown. These may be minor or severe. They may find out new risks while the study is going on. If this happens, the research staff will tell the participants any new information, whether it may affect her, and what, if anything, to expect.

Another risk of taking part in this study is the possibility of a loss of confidentiality. All efforts will be made to maintain confidentiality, including storage of data on secure servers and deidentification of data after it is collected.

2.10.2 Benefits

Participants may benefit from a reduction in blood pressure that could lead to lower rates of serious complications (e.g. seizure or stroke) as a result of participation in this study. There is, however, no guarantee that they will benefit from participation in this study.
Information learned from the study may help other people in the future.

2.10.3 Alternatives

Alternatives to participating in this study include non-participation.

2.10.4 Monitoring

To ensure safety of the subjects, local monitoring will be completed by the Quality Assurance Monitor for the Department of Obstetrics and Gynecology for this Investigator/Peer study. At each scheduled monitoring visit, the QA Monitor will randomly select a representative number of study subject charts to be reviewed. He/she will perform a data query and review electronically uploaded source records (admission/hospital note). Additional monitoring will be based on the initial monitoring review. Upon completion of monitoring, the QA Monitor will submit a report of his/her findings to Dr. Russell S. Miller (Principal Investigator), Dr. Ukachi Emeruwa (Lead Co-Investigator), Dr. Ronald Wapner (Vice Chair of Research/Innovation) and Michelle DiVito RN, MSN (Senior Director of Research Administration), with corrective actions if necessary.

The study will also be monitored by a Data Safety Monitoring Board (DSMB). The individuals responsible for monitoring data safety include:

1) Alexander Friedman MD, MPH, Associate Professor of Obstetrics & Gynecology and Maternal-Fetal Medicine specialist with expertise in large scale obstetrics outcomes-based research and care quality assessments
2) Dani Dumitriu MD, PhD Assistant Professor of Pediatrics (in Psychology) with expertise in basic science research, as well as Principal Investigator of multiple large scale and multidisciplinary studies investigating mother and baby outcomes
3) Alexander Melamed, MD, MPH, Assistant Professor of Obstetrics & Gynecology and Gynecologic Oncology specialist with expertise in harnessing large datasets to learn how to improve outcomes.

No member of the DSMB will have direct involvement in the conduct of the study, nor any financial or other interests with any of the collaborating organizations involved in the study that constitute a potential conflict of interest.

Meetings

The DSMB will convene as often as necessary, but at least three times annually (at 25%, 50%, and 75% enrollment), to examine the accumulated safety and enrollment data, review study progress, and discuss other factors (internal or external to the study) that might necessitate a protocol modification or impact continuation of the study as designed. A DSMB meeting may be requested by DSMB members, IRB, or study Principal Investigator at any time to discuss safety concerns (ad hoc meetings.) Meetings may be held by conference calls or videoconferences or as face-to-face meetings. In the event a DSMB member cannot attend a meeting, he/she may receive the DSMB report (see below) and either participate by conference call or provide written comments to the DSMB Chair for consideration at the meeting.

Specifically, the DSMB will review:

- any specific events that would preclude a participant from continuing the intervention
- any procedures in place for managing any medication-related issues – though this is a minimal risk study and we do not expect the following (e.g. allergic reactions, drug interactions, discontinuation/stoppage of medication)
- trial stopping rules for the study, if any (e.g. safety concerns, futility)
- any adverse events (non-serious and serious), unexpected safety events and unanticipated problems that occurred during study period

Reports and Recommendations

The DSMB will provide written minutes that identify topics discussed by the DSMB and describe its individual findings, overall safety assessment, and recommendations to the PI within a week of the meeting. Recommendations to discontinue or substantially modify the design or conduct of a study must be conveyed in a written, confidential report that may contain unmasked supporting data and include the DSMB member's rationale for their recommendations. It is the responsibility of the PI to forward the distributed communications from the DSMB to the IRB and other applicable entities.

The Principal Investigator and Lead Co-Investigator will also be responsible for monitoring the trial, starting at the point the patient begins the study drug in the hospital, the day of delivery. The patient will be given the research team contact information on the consent and instructed to report any concerns about or adverse effects from the study drug (Lasix/furosemide or placebo). Of course, in the case of any medical emergency, the patient will be cautioned to call 911. The medical members of the research team will make the determination of relationship of each adverse effect to the Lasix (furosemide). During the study, the Principal Investigator or study site personnel will be responsible for querying and recording adverse events and serious adverse events. All adverse events – regardless of seriousness or relationship to the study drug – occurring from the signature of informed consent through the period of study drug intake (within eight hours after delivery up to 5 days after delivery), should be recorded.

The research team will be keeping track of the patient's progress while she is recovering post-delivery, including blood pressures, labs, and post-procedural complications. If the patient develops any significant hypokalemia or severe renal dysfunction, which will be reflective in her labs, she will discontinue the drug. When the patient returns for her routine follow-up visit around 2 weeks and 6 weeks, the research team will follow up her postpartum course and monitor for any adverse events. If the patient is readmitted prior to her research follow-up visit, the research team will be notified by her clinical providers. The total monitoring period will last 6 weeks from the time of delivery. The entire clinical trial will be stopped if there is greater than expected morbidity from the study drug – that is, if multiple patients have to withdraw from the trial due to adverse effects from the Lasix (furosemide).

Once a mild adverse event is noted, the Principal Investigator will be notified by email within 1 to 2 days. If a moderate or serious adverse event or unanticipated problem arises involving risk to subjects or others, the Principal Investigator will be notified immediately by email. This information will then be relayed by the Principal Investigator to the appropriate monitoring and

regulatory entities, if needed. However, this is a minimal-risk study and such events are anticipated to occur very rarely.

2.11 Privacy and Data Security

2.11.1 Confidentiality of Study Data

Study subject numbers linked to patient MRNs will be stored on an excel file which will require a password to open, on the RedCap Server until the completion of data collection, after which all patient identifiers will be removed from the excel file. This password will only be known to Research Personnel. No hard copy will exist.

Data and research records will be primarily stored electronically in a study database on REDCap. This study database will be developed and maintained with support from Columbia University's Department of Obstetrics and Gynecology CORE Data Team.

REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. The system was developed by a multi-institutional consortium initiated at Vanderbilt University. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self- documenting process by all members of the research team with planning assistance from the OB/GYN Division of Research Informatics Support Team. The iterative development and testing process results in a well-planned data collection strategy for individual studies. With the assistance of the OB/GYN Division of Research Informatics, the research team work to maintain a software toolset and workflow methodology for electronic collection and management of research and clinical trial data.

REDCap servers are securely housed in an on-site limited access data center and is managed by the OB/GYN IT Division. The data is all stored on a private, protected university managed server. All users are authenticated via the CU and NYP LDAP servers and their access is restricted on a role-specific basis. Access can only be granted by administrators of the system. REDCap@OBGYN was developed specifically around HIPAA-Security guidelines and is implemented and maintained according to Columbia University and New York Presbyterian guidelines. All collected data are backed up daily. REDCap@OBGYN system id is 4283.

REDCap Reference:
P.A. Harris, R. Thielke, R. Taylor, J. Payne, N. Gonzalez, J.G. Conde. Research Electronic Data Capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics, 2008 (doi:10.1016/j.jbi.2008.08.010).

Source data will be stored on encrypted, password-protected servers maintained by OBGYN IT at the CUMC server farm; system id is 3959.

2.11.2 Privacy Protections

Patient information will be collected by trained research personnel in a private setting. Patient confidentiality will be maintained following HIPAA rules and regulations. Patients medical records will be accessed in a secure location by one of the research personnel. The MRN, name, study ID, and data variables will be recorded on the secure excel file mentioned above to obtain all data variables. At the completion of data collection all identifiable data will be removed from the research database. No patient identifiers (names, numbers etc.) will be recorded on hard copy paper.

3. References

1. Clark SL, Belfort MA, Dildy GA, Herbst MA, Meyers JA, Hankins GD. Maternal death in the 21st century: causes, prevention, and relationship to cesarean delivery. *Am J Obstet Gynecol.* 2008;199(1):36 e31-35; discussion 91-32 e37-11.
2. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. *Obstet Gynecol.* 2019;133(1):e1-e25.
3. Al-Safi Z, Imudia AN, Filetti LC, Hobson DT, Bahado-Singh RO, Awonuga AO. Delayed postpartum preeclampsia and eclampsia: demographics, clinical course, and complications. *Obstet Gynecol.* 2011;118(5):1102-1107.
4. Filetti LC, Imudia AN, Al-Safi Z, Hobson DT, Awonuga AO, Bahado-Singh RO. New onset delayed postpartum preeclampsia: different disorders? *J Matern Fetal Neonatal Med.* 2012;25(7):957-960.
5. Matthys LA, Coppage KH, Lambers DS, Barton JR, Sibai BM. Delayed postpartum preeclampsia: an experience of 151 cases. *Am J Obstet Gynecol.* 2004;190(5):1464-1466.
6. Sibai BM. Diagnosis, prevention, and management of eclampsia. *Obstet Gynecol.* 2005;105(2):402-410.
7. Lubarsky SL, Barton JR, Friedman SA, Nasreddine S, Ramadan MK, Sibai BM. Late postpartum eclampsia revisited. *Obstetrics and gynecology.* 1994;83(4):502-505.
8. Bigelow CA, Pereira GA, Warmsley A, et al. Risk factors for new-onset late postpartum preeclampsia in women without a history of preeclampsia. *Am J Obstet Gynecol.* 2014;210(4):338 e331-338 e338.
9. Chames MC, Livingston JC, Ivester TS, Barton JR, Sibai BM. Late postpartum eclampsia: a preventable disease? *Am J Obstet Gynecol.* 2002;186(6):1174-1177.
10. Ascarelli MH, Johnson V, McCreary H, Cushman J, May WL, Martin JN. Postpartum preeclampsia management with furosemide: a randomized clinical trial. *Obstetrics & Gynecology.* 2005;105(1):29-33.
11. Veena P, Perivela L, Raghavan SS. Furosemide in postpartum management of severe preeclampsia: a randomized controlled trial. *Hypertension in Pregnancy.* 2017;36(1):84-89.
12. Perdigao JL, Lewey J, Hirshberg A, et al. LB 4: Furosemide for Accelerated Recovery of Blood Pressure Postpartum: a randomized placebo controlled trial (FoR BP). *American Journal of Obstetrics & Gynecology.* 2020;222(1):S759-S760.
13. Atterbury JL, Groome LJ, Hoff C. Blood pressure changes in normotensive women readmitted in the postpartum period with severe preeclampsia/eclampsia. *J Matern Fetal Med.* 1996;5(4):201-205.

14. Hirshberg A, Downes K, Srinivas S. Comparing standard office-based follow-up with text-based remote monitoring in the management of postpartum hypertension: a randomised clinical trial. *BMJ Qual Saf.* 2018;27(11):871-877.