PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
Thomas McElrath, MD, PhD

PROTOCOL TITLE
A Randomized Controlled Trial Comparing Nifedipine and Enalapril in Medical Resources Used in the Postpartum Period

FUNDING
None

VERSION DATE
2/3/21

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

This project aims to determine if enalapril is superior to nifedipine at preventing prolonged hospitalizations, unplanned medical visits and/or readmissions in women with hypertension in the postpartum period. Our hypothesis is that women with hypertensive disorders of pregnancy randomized to enalapril as their primary antihypertensive will require fewer resources in the postpartum period than women randomized to nifedipine.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Hypertension is a common complication of pregnancy and the postpartum period and is responsible for a significant use of medical resources as women often require prolonged hospitalizations, unscheduled clinic visits and readmissions to control their blood pressure. (Stevens 2012, Clapp 2016) Many women may require antihypertensives to control it. Currently, at Brigham and Women's Hospital, we interchangeably use nifedipine, enalapril and/or labetalol to control postpartum hypertension. We do not know which medication is best, especially at preventing the use of extra medical resources. Nifedipine and enalapril are dosed daily so likely patients are more able to comply with treatment. We theorize that the mechanism of

action of enalapril is best suited for patients with hypertension in pregnancy as there appears to be a dysregulation of the renin-angiotensin-system. (Gant 1973)

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

This is an open-label randomized controlled trial in which participants will be randomized to receive either nifedipine or enalapril in the postpartum period for hypertension requiring antihypertensives. Women who are pregnant or recently postpartum (within 6 weeks) with hypertension can be recruited for the study. They must also be at least 18 years old and planning to follow-up at Brigham and Women's Hospital. They can be on no more than one antihypertensive and if they are, it must have been started in pregnancy. Women are not eligible for the study if they have any strict contraindications to nifedipine, enalapril or labetalol or a history of failed treatment with any of those agents. Their creatinine during admission must be less than 1.5. There will be 45 women recruited to each arm for a total of 90 women in the study. They will officially enter the trial once they are postpartum and their provider wants them to start or continue an antihypertensive.

All women will be enrolled by physician investigators or other physicians at Brigham and Women's Hospital who have agreed to help consent patients for this study. All patients will give written consent and will be informed that a licensed physician investigator is available to speak with them at any time during the consent process.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Patients who participate in the study will be randomized to receive nifedipine or enalapril in the postpartum period to control hypertension. The assigned antihypertensive should be titrated to control blood pressure so that systolic blood pressure is consistently less than 150 mmHg and diastolic blood pressure is consistently less than 95 mmHg. If a patient reaches 90mg daily of nifedipine or 40mg daily of enalapril without achieving this blood pressure goal or the patient's provider believes the assigned agent (nifedipine or enalapril) is ineffective, labetalol 200mg twice daily should be added to the regimen. Patients will follow-up in clinic in one week after discharge and six weeks for blood pressure checks and to have basic metabolic panels drawn.

At the six week visit, patients will be asked to complete a short survey. These are standard visits for postpartum patients. The study will be over once the patient has had her six-week postpartum visit.

The patient may be contacted via telephone by study staff to verify any additional interactions with outside hospitals or medical providers (which would influence the primary outcome).

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

There is no consensus on the best antihypertensive to use during the postpartum period. Currently at BWH, providers usually choose to use nifedipine, enalapril and/or labetalol to control postpartum hypertension as they are effective and safe during breastfeeding. The study procedures differ from standard care only in that it is formally randomized and not provider dependent.

There are alternative antihypertensives to use such as methyldopa or clonidine but these are rarely used at BWH.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

Risks to participants are minimized because the protocol is not deviating from standard care as we are giving medications that we would normally give in the postpartum period.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

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Patients will be monitored closely in the hospital and then in the postpartum period. We will monitor their vital signs and any symptoms or side effects they may have. We would remove a patient from the study if she has an adverse reaction to any of the antihypertensives such as significant hypotension, uncontrollable hypertension or intolerance of the medication. We will follow-up with these patients one week after they are discharged from their hospitalization and at six weeks postpartum.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

There is always the risk that the antihypertensive to which a participant is randomized will not work to control blood pressure or cause side effects.

We think there is minimal risk to our trial because these are all medications we routinely use in the postpartum period. We plan to carefully monitor patient's blood pressures and symptoms and providers will be able to titrate the antihypertensives and add additional antihypertensives if needed to control blood pressure.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

Because this study is a randomized controlled trial, there is no direct benefit to individuals. Given the nature of the study we do not know if, and which treatment is better. Furthermore, the study is randomly allocated so there is an equal chance of the patient being in either treatment arm. However, it is hoped that prescribing enalapril for postpartum women will decrease the frequency that women have prolonged hospitalizations, unscheduled clinic visits, triage visits or readmissions in the postpartum period by 30 percentage points.

This study will also ideally benefit women in the future. By determining which antihypertensive decreases the use of resources in the postpartum period (i.e. prolonged hospitalizations, unscheduled clinic visits, triage visits or readmissions), we will be able to help future patients by prescribing the antihypertensive that is best to minimize disturbances to their postpartum period. In addition, we will add to the limited body of knowledge regarding the use of ACE inhibitors in the postpartum period.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or

ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

Postpartum women with hypertension are the only group of women who will benefit from a study evaluating antihypertensives in the postpartum period. We are including all women who initially need a single antihypertensive to control their blood pressure in the postpartum period.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Non-English-Speaking-Subjects.pdf

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

Women will be enrolled from Labor and Delivery, the inpatient antepartum service or from the postpartum service. They will be identified by their diagnosis of hypertension. The patient's clinician will ask the patient permission to be approached by study investigators. Once permission granted, patients will be approached by physician investigators who will explain the study and obtain consent. If patients are recruited while they are pregnant, they will not enter the trial until they are postpartum and need an antihypertensive. If patients are recruited while they are postpartum, they will enter the trial once they need an antihypertensive.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Subjects will not be provided remuneration for participation in this study. Given that the study will occur in an admission and in routine postpartum visits, there will be no extra hospital visits, parking or meals.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Recruitment-Of-Research-Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Guidelines-for-Advertisements.pdf

Remuneration for Research Subjects
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Remuneration-for-Research-Subjects.pdf

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Patients will be consented on Labor and Delivery or during an inpatient admission for antepartum or postpartum care by the physician investigators. If a patient is still pregnant, she may consent to the study and will not formally be randomized until she is postpartum and her provider determines she needs an antihypertensive. If a patient is postpartum when she is consented, her provider may want to start antihypertensives shortly after she has been consented to the study. Therefore, pregnant patients may have several hours or days to decide if they want to participate in the study. Postpartum patients will likely have less than 1 hour to decide if they want to be in the study if their provider wants to start antihypertensives as it would be unsafe to delay treatment.

If a patient is approached to be in the trial by her own provider, there will be additional objective providers available from the inpatient Maternal Fetal Medicine team to talk with the potential participant about the study.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects:
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Informed-Consent-of-Research-Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

The principal investigator will review the entries for each participant to ensure they are complete. We will not have a data safety committee for this study given that we would not stop the study early because we feel there is minimal increased risk from the study protocol. Serious adverse events (including but not limited to cardiovascular events, severe allergic reaction, uncontrollable hypertension) will be reviewed by the head of labor and delivery, Julian Robinson MD, and the study staff to ensure the outcome is not related to study protocol. Dr. Robinson will serve as a safety monitor during the study.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

When adverse events occur they will be reported to the Partners' IRB within 5 days with a detailed description of the event, as assessment if the event is related to research and corrective actions, if applicable. Adverse events (including but not limited to cardiovascular events, severe allergic reaction, uncontrollable hypertension) will be reviewed by the head of labor and delivery and the study staff to ensure the outcome is not related to study protocol.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The data will be entered into a REDCap database. This will allow the principal investigator and study staff access to all the data. The quality of the data can therefore be assessed within the database. The principal investigator will review the entries for each case report. They will also review each informed consent to ensure it is adequately filled out in accordance with IRB protocol.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/DSMP-in-Human-Subjects-Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Reporting-Unanticipated-Problems-including-Adverse-Events.pdf

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical

record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

Each subject will be deidentified and given a study number. This study number will be linked to the MRN within the REDCap database but will be the only personal health identifier. The REDCap database will be limited only to study staff. This REDCap database has been used broadly within the Partners system as it is a password-protected database.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

No specimens or data will be sent to research collaborators for use outside of the Partners system.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

No specimens or data will be collected by research collaborators outside of Partners.