The University of Texas Medical Branch at Galveston

Research Protocol # 16-0280

Title: Postpartum management of hypertension in pregnancy with hydrochlorothiazide: a randomized clinical trial.
Principal Investigator: Benjamin Bush, MD
Funding: Departmental.

1. Introduction and Purpose:
Preeclampsia is a pregnancy complication that has serious repercussions to the mother and fetus. Currently at UTMB, postpartum women with gestational hypertension or preeclampsia are not routinely given hydrochlorothiazide for prophylaxis. Some providers use it in some patients, but it is a preference and not a standard of care as there is no clear evidence supporting it. Some, but not all, clinicians believe it improves blood pressure control postpartum and thereby reduces triage visits and hospital readmission. We are proposing to test this approach. We believe that postpartum HCTZ prophylaxis may prevent relapse of preeclampsia or gestational hypertension along with its associated co-morbidities. Our objective is to evaluate the effectiveness of hydrochlorothiazide prophylaxis on the readmission rates, need for additional antihypertensive medications and number of triage visits in women who are discharged following a diagnosis of pregnancy related hypertension.

2. Background:
In the developed world, hypertensive diseases are among the top three etiologies of maternal mortality. The incidence of hypertension in pregnancy is on the rise and it affects up to 10 percent of pregnancies. Hypertension also accounts for a large proportion of postpartum re-admissions, as well as maternal mortality and morbidity. Conflicting evidence exist as to whether early anti-hypertensive therapy in pregnant women with preeclampsia may be beneficial and shortens recovery time. However, despite being used at UTMB by some clinicians, data is lacking to support its prophylaxis use in postpartum women with preeclampsia/gestational hypertension.

3. Concise Summary of Project:
This will be a double-blind randomized placebo controlled clinical trial. Women who have delivered and have a diagnosis of gestational hypertension or preeclampsia will be approached for participation in the study, consented if they agree and meet the inclusion criteria.

The study's time frame will be from 2017 till 2023.
Subjects will be randomized to the following arms:

- *Study group*: Hydrochlorothiazide 50 mg per os once daily as soon as the subjects can tolerate sips of water after delivery and for a total of fourteen days postpartum.
- *Control group*: Placebo per os once daily as soon as the subjects can tolerate sips of water after delivery and for fourteen days postpartum.

Randomization will be performed by a person not involved in the clinical trial using a computer random list of numbers generated using STATA (StataCorp 14.0, Dallas, TX). This list of random

number assignments will be kept secure and sent directly to the investigational drug service (IDS), who will be responsible for the allocation and dispensing of the medications.

Both drug intervention and matching placebo will be purchased from Greenpark Compounding Pharmacy in Houston Texas (please see attached supplemental information for details).
Placebo formulation will contain same formulation of the drug pill but without the active pharmaceutical agent (Lactose, NF Monohydrate; Spray Dried).

We propose a total of 612 subjects will be needed to complete the study.
The subject will be withdrawn from the study if she wishes to discontinue participation.

4. Study Procedures:

After institutional review approval, eligible postpartum women will be approached to participate in the study. The study will be explained as in the consent form and if agreed subjects will elect either to participate or not after all risks and benefits are explained.

The data collected will be kept on a password-secured UTMB computer. An encrypted USB flash drive will be used to transfer data. The data will be linked to the subject by subject's MRN number. This identifier is needed to access and analyze demographic data. During analysis of the data, all identifiers will be deleted.

A total of three study visits will be encountered throughout the study:

VISIT#1

4.1 Screening, Recruitment and Consenting
Under the direction of the PI, trained research staff will be available 24/7 to screen and consent eligible subjects according to study protocol. Subjects will be enrolled in the postpartum period. If needed, a certified language interpreter will be available and Spanish consents will be used as appropriate. Medical records of all potential subjects with a diagnosis of preeclampsia or gestational hypertension will be reviewed and those who satisfy inclusion and exclusion criteria will be approached and a written informed consent will be obtained. Subjects will be recruited, enrolled and consented in a private room in labor and delivery or postpartum units in order to respect the privacy of potential subjects. Subjects will be given all the time needed in order to fully understand and read the consent forms. All efforts will be made by the research staff to answer all questions the subject has and to ascertain that subjects have the right to refuse to participate in the study. A screening log will be used to track all subjects approached for the study.

4.2 Randomization
A confidential computer-generated simple randomization scheme (using STATA 14, Dallas, TX) will be prepared. A randomization log with group assignment, subject name and medical record number will be used to track the randomization process. Randomization Sequence will be provided to the UTMB IDS pharmacy.

4.3. Disposal and Administration of Drug and Placebo

The intervention drugs (HCTZ and placebo) will be manufactured by Greenpark Compounding Pharmacy and shipped to UTMB's Investigational Drug Service (IDS). The latter will receive, store and dispense the drugs for the study.

Once a qualified subject is consented and randomized, an order will be entered in Epic. The UTMB IDS will be notified to dispense the study drug according to the treatment assignment and per study protocol and delivered to the nursing unit to be administered by the assigned nurse to the subject. The assigned nurse will document the administration in Epic using Medication Administration Record (MAR). Any unused study drug will be returned to IDS for documentation and disposal. Medications used in this study will not be billed to the subject or her insurance company.

The IDS will dispense the pills in a container/bottle and the subject will be given the bottle and given instructions to come to clinic at day 14 postpartum to see provider with bottle/container. The total supplies given will be enough for total treatment of 14 days.

The subject will be included in the analysis by intent-to-treat once the assigned pills are dispensed from IDS and sequential number posted on the subject specific randomization form.

Visit #2

Before the subject leaves the hospital, our research staff will be arranging the routine postpartum visit appointment and will document time and date in the datasheet, in order to ascertain follow up. The subject will be informed of the appointment and will be given a phone number for any questions and concerns regarding the study (Contact information are in the consents).

Visit #3

4.4. Study visits/Follow-up

Subject will be instructed to bring pill container to all clinic visits. The provider will document number of pills in the container in order to account for compliance. At the end of the treatment period, the research team will collect the container and count the returned pills prior to returning it to the IDS for reconciliation. Study participation will end at 6weeks postpartum. However, if subject does not come to their scheduled postpartum visits, we will do our best to attempt to contact and retrieve drug container up to 10 weeks postpartum.

If subject misses her regular postpartum visit we will make every effort to contact the subject by phone and enquire about the outcomes.

4.5. Baseline Procedures

Routine postpartum care will be provided by the subjects' clinical providers.

Trained and experienced research staff will be responsible for all research data abstraction.

The PI will review and validate the diagnosis for all subjects identified to have the primary outcomes. These reviews will be conducted masked to treatment group. If there is uncertainty, research staff will review the chart, discuss with the PI as needed and make a final determination regarding the outcome.

Several data collection forms will be used during these processes. Data on these forms, devoid of personal identifiers, will be securely stored at our perinatal research division. Data to be collected will consist of demographics, obstetrical history, rate of admission or triage visits, relevant vital signs and laboratories.
Examples of data to be collected but not limited to include: total dose of anti-hypertensives used, peak systolic blood pressure at discharge, peak mean arterial pressure at discharge, peak diastolic blood pressure at discharge, hospital length of stay, use and total dose of additional antihypertensives, blood pressures at the routine postpartum care visit (normally in general 1-3 weeks after delivery), maternal morbidity (death, pulmonary edema, stroke, acute kidney injury, recurrence of preeclampsia).

4.6. Withdrawals

Subjects who withdraw from the study after randomization will be excluded from further follow-up. Outcomes ascertained up until the time of withdrawal will be reported in an intent to treat fashion. Those who withdraw prior to determining the primary outcome will be accounted for by randomizing an equal number of additional subjects.

4.7 Outcomes

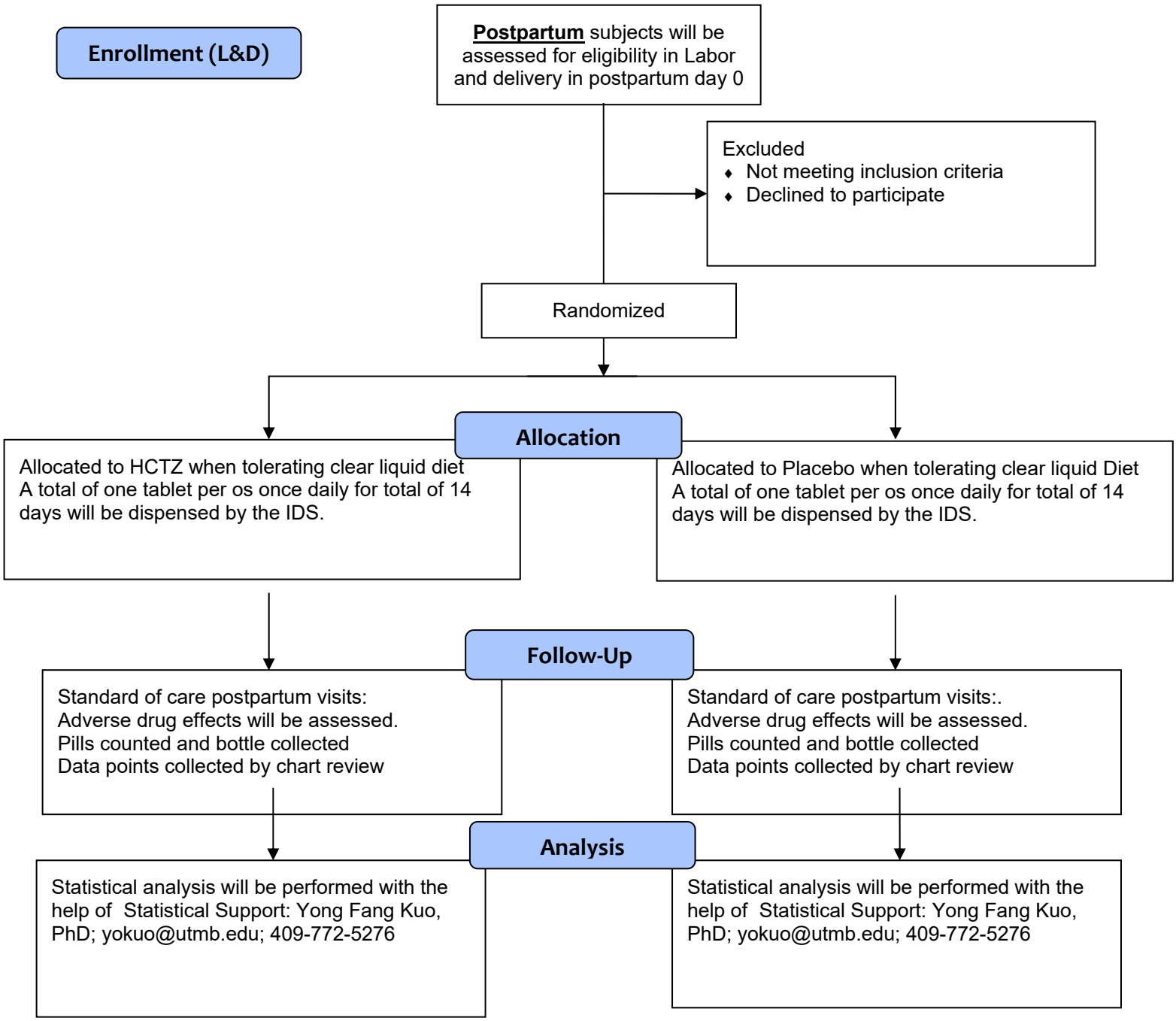
Primary outcome:

- Rate of readmission or triage visits.
- Requiring additional anti-hypertensive drugs.

Secondary outcomes:

- Hospital length of stay.
- Use and total dose of additional antihypertensives.
- Elevated Blood pressures at the regular postpartum visits (normally 1-6 weeks after delivery) >150/90
- Severe composite maternal morbidity [Time Frame: 0-6 weeks after delivery]
    - Any of the following: ICU admission, HELLP syndrome, eclampsia, stroke, renal failure, pulmonary edema, cardiomyopathy or maternal death
- Use of resources: hospital stay, postpartum clinic or emergency room visit within 4-6 weeks of delivery, need for imaging or other invasive procedures.
- Adverse events: allergic reactions (anaphylaxis, angioedema, skin rashes including Stevens Johnson and Toxic Epidermal necrolysis).

HCTZ Study Flow Diagram



5. Criteria for Inclusion of Subjects:

- Maternal age ≥ 18 years and <50 years.
- Diagnosis of gestational hypertension* or preeclampsia^ at any time during pregnancy, labor or postpartum.

  *defined as isolated systolic BP of 140 mm Hg or greater, a diastolic BP of 90 mm Hg or greater, or both) or
  ^ defines as new-onset hypertension plus new-onset proteinuria, or in the absence of proteinuria, preeclampsia is diagnosed as hypertension in association with thrombocytopenia (platelet count less than 100,000/microliter), impaired liver function (elevated blood levels of liver transaminases to twice the normal concentration), the new development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dL or a doubling of serum creatinine in the absence of other renal disease), pulmonary edema, or new-onset cerebral or visual disturbances.)

6. Criteria for Exclusion of Subjects:

- Subject requiring antihypertensive therapy at time of screening.
- Planned discharge with oral anti-hypertensive medication.
- Contraindication to hydrochlorothiazide (advanced renal failure or anuria, hypersensitivity to sulphonamides).
- Subject not able to follow up postpartum.
- Lactose intolerance.
- Pregestational diabetes.

7. Sources of Research Material:

Electronic Medical chart/records

8. Potential Risks:

8.1 Drug adverse events

Subjects who are given Hydrochlorothiazide may have the following:

Frequent

- Electrolyte imbalances especially low blood potassium and less commonly low blood sodium
- Low blood pressure

Occasionally

- Stomach cramps
- Diarrhea
- Nausea/vomiting

Rare

- High blood sugar
- Feeling faint initially upon standing up

Serious but Rare

- Glaucoma (increase pressure in eye)
- Gout (large toe pain)
- Allergic Reaction

According to the NIH Lact med database: Doses of HCTZ 50 mg daily or less are acceptable during lactation. Intense diuresis with larger doses may decrease breastmilk production (Reference: https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~o2KQrh:1).

If any of these risks occur, subjects will be managed according to standard of care based on the symptoms and signs/complaints.

8.2 Randomization risk

Since treatment will be randomized, it is possible that one or more of the other treatment groups will have more benefit or lower side effects than the group to which subject is assigned.

8.3 Loss of Confidentiality

Anytime information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep subject's information confidential; however, this cannot be guaranteed.

9. Procedures to Maintain Confidentiality:

The data collected will be indirectly linked to the subject by subject's MRN number.
When the subject agrees to participate in the study, a subject number will be assigned to the subject - from 1 to 612 - and this number will be entered on the data collection sheet.
The data collected will be transferred to the PI's password-secured UTMB computer that is stored in a locked room using a USB flash drive.
The study PI will be the only person to have a list with the number designated to each subject and the corresponding subject's MRN number. This list will be kept in a locked cabinet of the PI's locked UTMB office. This identifier is needed to access and analyze demographic data. During analysis of the data, all identifiers will be deleted.
Data will not be disclosed to outside persons or entities.

10. Potential Benefits:

This study may show that early prophylactic treatment with Hydrochlorothiazide in subjects with preeclampsia will decrease need for readmission in the postpartum period, and prevent maternal morbidity. Ultimately, this will reduce the health care costs associated with shortened length of stay and decreased readmissions.

11. Biostatistics:

Analysis will be performed by intent to treat. Univariate analysis will be used to describe the population in the study. For this analysis normality will be tested using Shapiro-Wilk method. Demographics will be analyzed by descriptive statistical methods such as Student t test, Pearson's chi square, and Mann-Whitney tests as appropriate. Data will be either shown as median +/- IQR or mean +/- SDEV. Statistical analyses of primary and secondary outcomes between two groups will be performed by chi square test. Relative risk and 95% confidence intervals will be calculated. Sample size was calculated using a superiority trial design. The primary outcome will be the occurrence of triage visit or hospitalization or requiring additional anti-hypertensive medications, which will be compared between the two study groups. From the available data FROM UTMB of the rate of revisit to triage/hospitalization/clinic at 15% in our facility, with alpha =0.05 and power of 80% and to detect a 50% difference our estimated total sample size was 556.

To account for a 10 percent loss to follow up, total number of subjects: 612. Detailed below: We used the Pearson's chi-squared test : Ho: p2 = p1 versus Ha: p2 != p1 Study parameters: alpha = 0.0500; power = 0.8000; delta = -0.0750 (difference) proportion1 = 0.1500; propotion2 = 0.0750 Estimated sample sizes: N = 556; N per group = 278

Bayesian Analysis Plan

At the time of study completion or study closure due to feasibility or slow recruitment, we will conduct a Bayesian analysis to ascertain robust estimates of the study parameters. Bayesian analysis offers a flexible approach that allows for incorporating prior knowledge into the analysis, which may be particularly useful given the potential for low recruitment and smaller sample sizes. Given the data collected, This analysis will estimate the probability that our hypotheses are true.

1. Prior Information
We will carefully select our prior distributions based on available information from previous studies and expert opinions. This prior information will be explicitly stated and justified in our final report to ensure transparency. Without relevant prior information, we will use non-informative or weakly informative priors.

2. Likelihood Function
We will calculate the likelihood based on the collected data. Given the different parameter values under consideration, this likelihood reflects how probable our observed data is.

3. Posterior Distribution
We will then combine the prior and the likelihood to obtain the posterior distribution using Bayes' Theorem. After considering the collected data, the posterior distribution provides us with updated beliefs about the parameter values.

4. Model Comparison and Validation
We will compare different models using Bayesian model comparisons methods, such as Bayes Factors or the Deviance Information Criterion (DIC), to determine which model best fits our data. We will also use posterior predictive checks to ensure our model fits the data well.

5. Reporting of Results
The results will be reported as a distribution of plausible values (posterior distribution) rather than a single estimate. We will provide point estimates, such as the mean or median of the posterior distribution, along with a measure of uncertainty, such as a credible interval.

12. Subject Safety and Data Monitoring:

The PI and research collaborators will be responsible for monitoring the safety of this study. The yearly report will include participant demographics, expected versus actual recruitment rates, summary of any quality assurance or regulatory issues, summary of adverse events (AEs) or serious adverse events (SAEs) which may have occurred, and any changes in the protocol as a result of these issues.

The PIs and collaborators will ensure all aspects of data quality including monitoring for adherence to consent procedures, inclusion and exclusion criteria, valid abstraction, correct entry, timeliness and responsiveness to data queries.

Data will be collected and stored with the participant ID code only. The master enrollment log linking subject identifiers with study ID numbers will be kept in a password-protected database on the Ob/Gyn Department's internal server separate from the data. Several data collection forms will be used. Data on these forms devoid of personal identifiers will be securely stored at our perinatal research division. The research coordinator will be available to monitor the data and correct any discrepancies based on source documents if needed.

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