Title: ASPPIRE - Aspirin to Prevent Preeclampsia in Women with Elevated Blood Pressure and Stage 1 Hypertension

Date: 12/08/2021

Clinicaltrials.gov ID: NCT04402385

Document: Protocol w SAP

HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: ASPPIRE - Aspirin to Prevent Preeclampsia in Women with Elevated Blood Pressure and Stage 1 Hypertension

Principal Investigator: Olga Grechukhina, MD
Sub-Investigators: Victoria Greenberg, MD; Moeun Son, MD, MSCI; Heather Lipkind, MD, MPH

Version Date: 12/08/2021

Clinicaltrials.gov Registration #: NCT04402385

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.
   To determine if low dose aspirin reduces the incidence of hypertensive disorders of pregnancy (gestational hypertension, preeclampsia, eclampsia, and HELLP syndrome) in pregnant women with stage 1 hypertension and elevated blood pressure.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.
   5 years

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

New hypertension guidelines proposed in 2017 by the American College of Cardiology/ American Heart Association (ACC/AHA) redefined blood pressure (BP) categories as Stage 1 hypertension (systolic 130-139 mmHg or diastolic 80-89 mmHg), Elevated (systolic 120-129 mmHg and diastolic <80mm) and Normal (<120/<80 mmHg). Adaption of these new definitions increases the prevalence of hypertension among adults in the United States by approximately 31 million people. Since publication of the updated guidelines, several studies have assessed lower levels of blood pressure elevations and subsequent pregnancy outcomes.

A secondary analysis of a large, prospective study of nulliparous women evaluated both first trimester blood pressure categories and blood pressure trajectories from the first to second trimester. A total of 8,899 nulliparas were included in this secondary analysis. Increasing first trimester blood pressure category was associated with higher risk of all hypertensive disorders of pregnancy. Elevated blood pressure was associated with an adjusted relative risk of 1.54 (95% confidence interval, 1.18, 2.02) and stage 1 hypertension was associated with adjusted relative risk of 2.16 (95% confidence interval, 1.31, 3.57) of any hypertensive disorder of pregnancy. Stage 1 hypertension was associated with the highest risk of preeclampsia with severe features, with an adjusted relative risk of 2.48 (95% confidence interval, 1.38,8.74).

In a secondary analysis of a multicenter randomized controlled trial examining the effects of aspirin for preeclampsia prophylaxis, women with Stage 1 hypertension (systolic blood pressures 135-139 and/or diastolic blood pressure 85-89) were compared with normotensive women. In women randomized to placebo, 15% had preeclampsia if they had stage 1 hypertension compared to 5% of those who were normotensive. The study also found that women with stage 1 hypertension had increased rates of indicated preterm deliveries and gestational diabetes. The women in this study with stage 1 hypertension had a 40% risk reduction of developing preeclampsia when they took aspirin 60mg daily compared to placebo.

In a large study of women with prehypertension, defined as two consecutive elevated blood pressures (systolic 120-129 mmHg or diastolic 80-89 mm Hg) in the 12 months prior to last menstrual period up to 12 weeks gestational age, there was a two-fold increased rate of hypertensive disorders of pregnancy. In a cohort of 7,802 women within the Kaiser Permanente health system, 28% had prehypertension. Women with prehypertension were 2.65 times more likely to develop a hypertensive disorder of pregnancy, 2.17 times more likely to develop preeclampsia, and 1.2 times more likely to develop gestational diabetes as compared to normotensive women.

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

Studies of reproductive-aged women show that twice as many women will be diagnosed with hypertension prior to pregnancy (18.9% vs 10.2%) with the new ACC/AHA guidelines. Lowering the blood pressure threshold for hypertension from 140/90 has unknown implications for pregnant women. While the new guidelines propose non-pharmacologic management of stage 1 hypertension, pregnancy management could be significantly affected by the new guidelines.

Multiple randomized controlled trials and meta-analyses have demonstrated the beneficial effects of preeclampsia prophylaxis with aspirin in women at high risk of developing preeclampsia. High risk factors include a prior history of preeclampsia, chronic hypertension, and pre-gestational diabetes.

Low-dose aspirin is safe for use in pregnancy. Multiple large cohort and case-control studies have not found an association with congenital defects, structural, or developmental anomalies in the fetus. Use in the third trimester does not cause premature closure of the ductus arteriosus. Maternal use is safe without an increased risk of bleeding. There is no increased risk of gastrointestinal bleeding, placental abruption, epidural hematoma, and postpartum hemorrhage. Timing of aspirin use to decrease the risk of preeclampsia is important. Earlier initiation appears to be beneficial, with a large meta-analysis indicating optimal effects when initiated before 16 weeks of pregnancy. The EAGeR trial, which randomized women to low dose aspirin or placebo prior to conception, demonstrated similar livebirth rates and no increase in adverse safety events between the groups. The ASPRE trial randomized women at high risk for preeclampsia to aspirin versus placebo in the first to early second trimester (11-14 weeks' gestation) with reduction seen in preeclampsia.

To date, there are no randomized controlled trials of preeclampsia prophylaxis with aspirin in women with elevated blood pressure or stage 1 hypertension (by 2017 ACC/AHA guidelines), and no other high-risk predictors of preeclampsia.

Stage 1 Hypertension increases risk of preeclampsia:

- Sutton, Caritis, et al 2018). Maternal outcomes associated with lower range stage 1 hypertension. *Obstet Gynecol 132(4),* 843-849
    - This is a secondary analysis of a randomized controlled trial across 7 centers in the United States that enrolled nulliparous women with BP >135/85) to aspirin 60mg or placebo between 13-25 weeks of pregnancy
    - This secondary analysis looked at a subset of women (164 of the initial 3,134 were found to have stage 1 hypertension)
    - Among women receiving placebo, preeclampsia occurred significantly more often in women with stage 1 hypertension compared with normotensive high-risk women after adjustment for maternal age and body mass index (39.1% versus 15.1%; risk ratio, 2.49; 95% confidence interval, 1.74–3.55).
    - Women with stage 1 hypertension had a significant risk reduction related to aspirin prophylaxis (risk ratio, 0.61; 95% confidence interval, 0.39–0.94) that was not seen in normotensive high-risk women (risk ratio, 0.97; 95% confidence interval, 0.70–1.34).
- Black MH et al (2015). Prehypertension prior to or during early pregnancy is associated with increased risk for hypertensive disorders in pregnancy and gestational diabetes.
    - This study: 10,459 women between 2005-2010 with ICD-9 codes used to identify hypertension and pre-hypertension in the 12 months prior to pregnancy and through 12 weeks gestation
    - 2,156 (27.6%) women had pre-hypertension. More likely to be older, white or black, obese, gain excess weight during pregnancy, and to develop GDM

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

        - ICD codes used to identify preeclampsia and gestational hypertension
        - Women were diagnosed with pre-hypertension if they had 2 consecutive elevated BPs (SBP >120 and/or DBP >80)
        - Results: 653 (8.4%) developed hypertensive disorder of pregnancy
    - 2.65 times more likely to develop hypertensive disorder of pregnancy and 2.17 times more likely to have PEC/eclampsia than normotensive women after adjustment

Aspirin reduces risk of preeclampsia:

- Luley D, Meher S, Hunter KE, Seidler AL, & Askie LM (2019). Antiplatelet agents for preventing preeclampsia and its complications. *Cochrane Database of Systematic Reviews.*
    - Meta-analysis of 77 trials including 40,249 women to evaluate placebo versus placebo in preeclampsia risk reduction
    - 9 of the 77 trials included >1,000 women in each. This contributed to 80% of the included patient population.
    - Low dose aspirin dosages varied from 50mg to 150mg daily
    - In total, aspirin reduced the risk of preeclampsia by 18% with a number needed to treat of 61 women to prevent one case of preeclampsia
- Caritis S, Sibai B et al (1998). Low-dose aspirin to prevent preeclampsia in women at high risk. *NEJM, 338:*701-705
    - RCT of aspirin 60mg or placebo begun at 13-26 weeks in women with high risk features (prior PEC, cHTN, pre-gestational diabetes, multifetal gestations)
    - Adherence: did 1 week of placebo first, only included women who took >50%. Then had phone follow-up with research nurse
    - No improvement with LDA
- Odibo AO, Goetzinger KR, Odibo L, & Tuuli MG (2015). Early prediction and aspirin for prevention of pre-eclampsia (EPAPP) study: a randomized controlled trial. *Ultrasound in Obstetrics and Gynecology, 46:* 414-418
    - Randomized controlled trial of women receiving low dose aspirin if they had one or more high risk factors for developing preeclampsia
    - Aspirin dispensed by the pharmacy
    - Pill diary done by patients, then asked to return unused pills to be counted by the pharmacy
    - Study concluded early due to clinical equipoise and new societal guidelines recommending aspirin in women with at least one high risk factor for preeclampsia
    - Study ended with 53 women, 30 of them randomized to receive aspirin
    - No differences found in rates of preeclampsia between the groups
- Byaruhanga RN, Chipato T, & Rusakaniko S (1998). A randomized controlled trial of low-dose aspirin in women at risk from pre-eclampsia. *International Journal of Obstetrics & Gynecology, 60*(2): 129-135
    - 75mg versus placebo in 250 women with prior history of PEC or cHTN
    - Received container with 126 tablets. Asked about adherence at each visit. Monthly count of remaining tablets. Total adherence if 80% or more tablets taken
    - No significant difference found in rates of preeclampsia between the groups

Aspirin timing for preeclampsia prophylaxis

- Roberge S, Bujold E, Nicolaides KH. Meta-analysis on the effect of aspirin use for prevention of preeclampsia on placental abruption and antepartum hemorrhage. Am J Obstet Gynecol 2018, 218(5): 483-489

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

  - Aspirin dose <100mg daily when initiated prior to 16 weeks decreases risk of placental abruption or antepartum hemorrhage compared to initiation after 16 weeks
- Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gyneol 2018, 218(3): 287-293
  - Meta-analysis of 16 trials including 18,907 women analyzing outcomes of preeclampsia in women randomized to aspirin (at varying doses) versus placebo
  - No reduction seen in term preeclampsia
  - Reduction in preterm preeclampsia when initiated before 16 weeks' gestation
- Meher S, Duley L, Hunter K, Askie L. Antiplatelet therapy before or after 16 weeks' gestation for preventing preeclampsia: an individual participant data meta-analysis. Am J Obstet Gynecol 2017, 216(2): 121-128
  - Individual participant data meta-analysis including 31 randomized controlled trials with 32,217 women comparing aspirin or other antiplatelet therapy versus placebo for preeclampsia prevention
  - Subgroup analysis looking at timing of aspirin initiation (before or after 16 weeks)
  - Found consistent reductions in preeclampsia, preterm birth <34 weeks, small for gestational age neonate, and stillbirth regardless of when the dose was initiated
- Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med 2017, 377: 613-622
  - Randomized controlled trial of 1,776 women with high risk factors for preeclampsia given aspirin 150mg versus placebo daily for preeclampsia prevention
  - Initiated between 11-14 weeks' gestation
- Committee on Obstetric Practice, Society for Maternal-Fetal Medicine. ACOG Committee Opinion: Low-dose aspirin use during pregnancy. Obstet Gynecol 2018, 132(1): e44-e52
  - Society guidelines for initiation of low dose aspirin between 12-28 weeks' gestation, optimally before 16 weeks' gestation

4. Research Plan:

Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

Setting: Maternal-Fetal Medicine office at academic center; Women's Center (academic resident-run obstetric clinic); private office for patients with university insurance, and private OBGYN offices that deliver at Yale New Haven Hospital

1. At the baseline visit, women will go through informed consent and review of study eligibility. Objectives of the study, participation requirements, eligibility inclusion and exclusion will be reviewed in detail. We will complete checklist of inclusion criteria. If these are not met, the woman is excluded from the study. If she meets inclusion criteria, a checklist of exclusion criteria will be reviewed. If any exclusions are met, the woman is excluded from the study. The consent form will be reviewed in detail. If the woman consents and signs all pages of the form, randomization follows.

Randomization will be done in a 1:1 allocation ratio between the treatment and placebo arms. A computer algorithm will assign participant based on random permuted blocks design with block size between 2-4. Each participant will have an assigned Study ID number that is linked to their random assignment. Two staff members will know the randomization allocation. One staff member will be in the Yale Investigational Drug

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

Services (IDS) and will not have any further part in the study. The second study unblinded study member will be Lauren Perley, an experienced research nurse within the Maternal-Fetal Medicine division. Remote dispensing has been approved by Jing Lu of the Yale IDS.

In order to improve patient recruitment, our office will perform remote dispensing as per ASHP guidelines (document included in IRB re-submission). This includes temperature monitoring to maintain room temperature at 20-25 degrees Celsius utilizing an approved temperature monitoring system and temperature logging. We will also maintain drug accountability logs. All logs and regulations are submitted as documents to this IRB.

Yale IDS will continue to compound our study medications and dispense pre-counted and bottled medications labeled with study participant ID number as per the randomization scheme. This randomization scheme is shared with our staff member, Lauren Perley, who will dispense the pre-bottled study medications to study participants as per the study ID number. All allergies and co-morbidities will be verified by research staff. Labeling of medications will be performed by Lauren Perley.

Based on the participant assignment, we will dispense enough medication for the rest of the pregnancy. The bottles of study medication are pre-packaged and identical in appearance.

The patient and the rest of the research staff personnel are blinded to study allocation. The staff members who are unblinded will not be involved in data acquisition, statistical analysis, and paper writing. Yale IDS will dispense study medication at the time of randomization. Yale IDS will perform pill counting at the beginning and completion of study enrollment in order to assess patient adherence with the regimen. Medication adherence may be encouraged by helping participants to set a daily reminder on their phone or calendar.

*2. Participants will be contacted by telephone **1 week** after randomization. The purpose of this visit is to ensure the participant has received study medication and initiated the regimen. We will then discuss any side effects, questions, and/or concerns about the study. Any problems will be discussed and mitigated if possible.*

3. The third encounter will be 6 weeks (+/- 1week) after randomization in person to coincide with routine prenatal visit or via telephone. The purpose of this study visit is to review their pregnancy course, use of study medications, any side effects, difficulties with the study, and have opportunities to make comments and/or ask questions. The participants will be asked to bring their study medication for pill count at the time of this encounter, if the study visit is able to be performed in person. Study participants will continue their routine prenatal care with pregnancy management performed routinely per their provider.

4. The fourth encounter will be 16 weeks (+/- 1week) after randomization in person to coincide with routine prenatal visit or via telephone. If the participant is already delivered by this time, the visit will be performed via telephone postpartum. The purpose of this study visit is to review their pregnancy course, use of study medications, any side effects, difficulties with the study, and have opportunities to make comments and/or ask questions. The participants will be asked to bring their study medication for pill count at the time of this encounter, if the study visit is able to be performed in person.

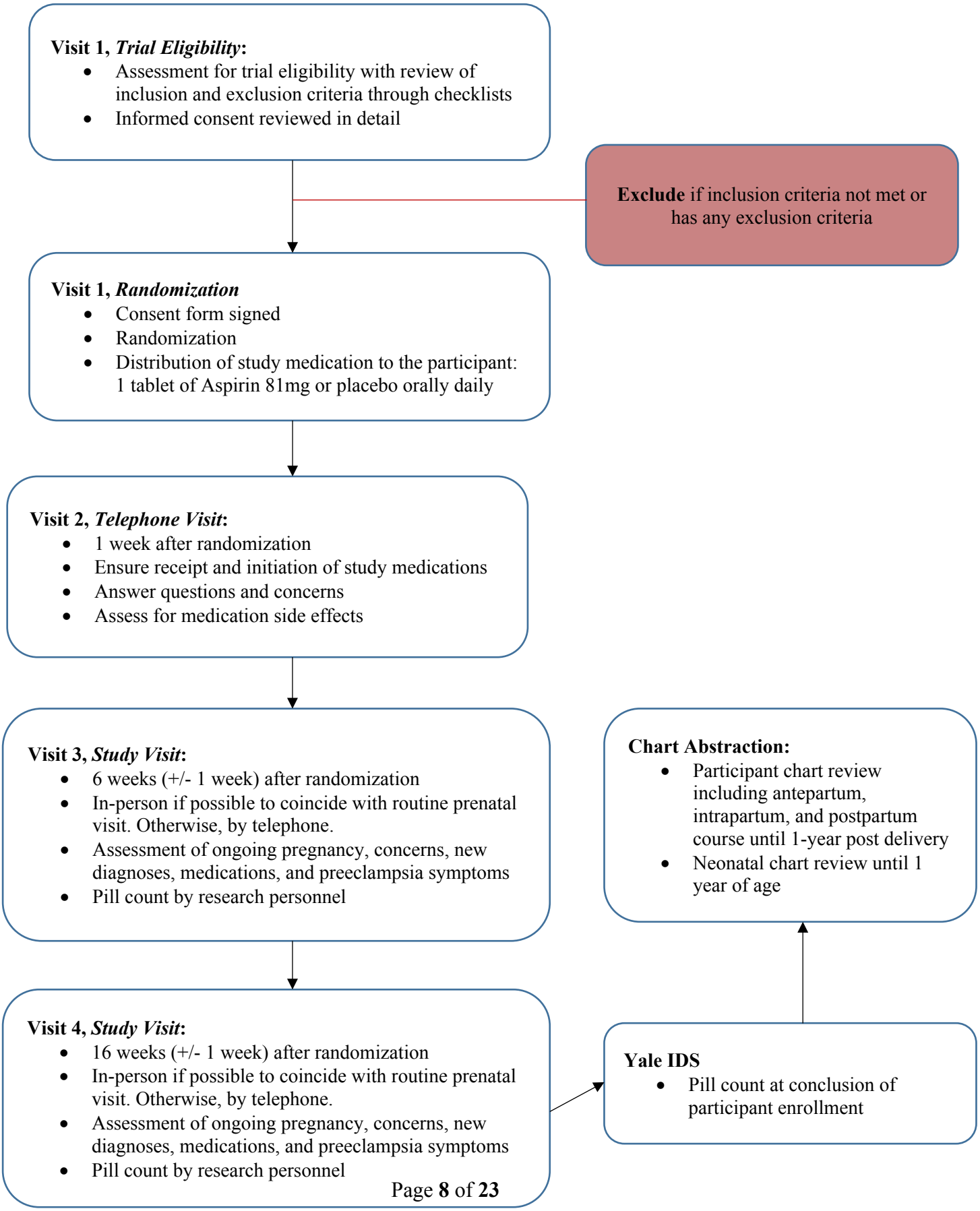
5. The rest of the study will be conducted via chart review. Each prenatal visit will be reviewed for blood pressure, evaluation of symptoms, review of any laboratory and/or imaging results. New diagnoses, medications, and hospital admissions will be documented.

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

6. Delivery records will be abstracted for outcomes listed below. Neonatal records will be reviewed from birth until 1 year of age. Neonatal and infant chart abstraction will include birthweight, Apgar scores, hospital course, problem visit, diagnoses, medications, emergency department visits, and hospitalizations. Participant's postpartum course will be reviewed for 1 year postpartum, including outpatient visits, emergency department visits, and any hospitalizations.

The study will be performed by an intent-to-treat analysis. Thus, even women who discontinue study medication will be included in final analyses.

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021



APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

5. Genetic Testing N/A ☒

6. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.
Pregnant women ages ≥ 18 years with live, singleton pregnancies enrolled prior to 20 weeks gestational age. These women will receive prenatal care through a Yale New Haven Hospital (YNHH)-associated obstetric and/or midwifery practice. They will plan to deliver at a hospital within the YNHH system.

7. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☒Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☒Pregnant women and/or fetuses
☐Yale Students	☒ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

8. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion:

- Age ≥ 18 years
- Singleton pregnancy
- Elevated blood pressure (At least 2 systolic BP 120-129 mm Hg within 1 year pre-pregnancy until 20 weeks gestational age on at least 2 separate healthcare encounters) or Stage 1 hypertension (At least 2 systolic BP 130-139 and/or diastolic BP 80-89 within 1 year pre-pregnancy until 20 weeks gestational age on at least 2 separate healthcare encounters)
- Speaks English or Spanish
- Informed and written consent
- Confirmed single live intrauterine pregnancy (confirmed by positive cardiac motion by transvaginal or transabdominal ultrasound)

Exclusion:

- Chronic hypertension
- Pre-gestational diabetes, defined as diabetes diagnosed prior to pregnancy (type 1, 1.5, or 2)
- Chronic renal disease
    - diagnosis of stage 1 chronic kidney disease or higher and/or GFR <60 mL/min with duration at least 3 months and/or history of kidney transplantation and/or undergoing peritoneal or hemodialysis
- Systemic lupus erythematous
- Antiphospholipid antibody syndrome
    - diagnosis made by having 1 or more clinical criteria and 1 or more laboratory criteria

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

    - Clinical criteria: venous thrombosis, arterial thrombosis, obstetric complications (3 or more unexplained consecutive spontaneous abortions <10 weeks gestation, 1 or more unexplained deaths of a morphologically normal fetus after 10 weeks gestation, 1 or more premature births before 34 weeks gestation attributable to placental insufficiency, including severe preeclampsia or fetal growth restriction)
    - Laboratory criteria: lupus anticoagulant, anti-cardiolipin IgG or IgM with titer >99th percentile, anti-beta 2 glycoprotein IgG or IgM with titer >99th percentile. Laboratory result must be positive twice at least 12 weeks apart
- Multifetal gestation
- ≥ 20 weeks gestation at time of randomization based on American College of Obstetricians and Gynecologists dating criteria. Dating will be based on last menstrual period (LMP) if regular, sure LMP is available that agrees with ultrasound dating. Otherwise, earliest ultrasound will be used for dating purposes.
- Prior history of hypertensive disorder of pregnancy
- Current pregnancy with known chromosomal, genetic, major malformations or fetal demise, or planned termination of pregnancy
- Women with contraindications to taking aspirin (bleeding diathesis such as Von Willebrand's disease, peptic ulcer disease, aspirin hypersensitivity, nasal polyps, asthma with aspirin-induced bronchospasm, severe liver disease).
- Concurrent participation in another study that influences risk of preeclampsia
- Women who do not plan to deliver within the YNHH system

Write here

9. How will **eligibility** be determined, and by whom? Write here

Eligibility will be determined by study personnel with human subject protection training and ability to randomize patients. Patients will be approached and asked about eligibility criteria utilizing a checklist. If any exclusion criteria are met, the patient will not be eligible to participate in the study.

An MFM or OBGYN attending will confirm that the woman has a single, live intrauterine pregnancy by transvaginal or transabdominal ultrasound as part of standard of care. This ultrasound typically occurs between 8-14 weeks gestational age. The results of this ultrasound will be recorded in the woman's electronic medical record and this documentation will serve to confirm that this eligibility criterion has been met.

Women will be deemed to have elevated blood pressure if they have at least 2 systolic blood pressure measurements of 120-129 mm Hg within 1 year prior to pregnancy until 20 weeks gestational age on at least 2 separate healthcare encounters. Women will be deemed to have stage 1 hypertension if they have had at least 2 systolic blood sure measurements of 130-139 mm Hg and/or diastolic blood pressures of 80-89 mm Hg within 1 year prior to pregnancy until 20 weeks gestational age on at least 2 separate healthcare encounters.

Enrolled participants will be randomized after a single, live intrauterine pregnancy is determined by ultrasound. They must then be randomized prior to 20 weeks' gestation.

10. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Risks of aspirin:

- Most common: stomach upset, heartburn, nausea, vomiting (likelihood: 1-3/100 people)

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

- Uncommon: Gastrointestinal bleeding (likelihood: 0.5-3/1,000 people)
- Rare but serious: Acute renal failure, hives or facial swelling (likelihood: 7-20/10,000 people), bleeding in the brain (likelihood: 4/10,000 people)
- Contraindicated in people with: bleeding disorders (such as Von Willebrand's Disease), peptic ulcer disease, nasal polyps, asthma with aspirin-induced bronchospasm, severe liver disease, and aspirin or salicylate allergy or hypersensitivity.
- Breach of confidentiality. This is mitigated by having name and phone number of the patient visible to only two research staff members. After completion of the study and information collection, identifiers will be removed and be exchanged with a code number. The information is kept in a password-protected database via Yale's RedCap system. These files will only be accessed by a small group of research staff. Consent form documents will be kept in a locked cabinet in our research office, accessible only by Yale Maternal-Fetal Medicine research staff. Publications and presentations will not include any names or identifying information.

11. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.
We will ensure that patients with the listed contraindications to aspirin therapy are not enrolled in the study. Low dose aspirin (81mg) with enteric coating will be used, which will reduce the gastrointestinal side effects. While gastrointestinal bleeding is possible, it is very unlikely at this low dose.
Patients will be provided a list of medications containing salicylic acid so they do not take any in addition to the low dose aspirin.

12. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? *Greater than minimal risk*
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? *N/A*
    c. Include an appropriate Data and Safety Monitoring Plan:

    Greater Than Minimal Risk DSMP

    1. Personnel responsible for the safety review and its frequency:

    The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which will be conducted every 6 months. The first DSMB is scheduled for May 2021. During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

    An independent data safety monitoring board will be constructed, consisting of three members outside of Yale University who are not co-investigators on the trial. Two of these members will be obstetricians and one a biostatistician.
    Either the principal investigator or the IRB have the authority to stop or suspend the study or require modifications.

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

2. The risks associated with the current study are deemed greater than minimal for the following reasons:

1. We do not view the risks associated with the experimental arm as minimal risks.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:
Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator and Victoria Greenberg, MD according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:
In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:
Any incident, experience or outcome that meets ALL 3 of the following criteria:
1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized. Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – serious, unexpected, and related adverse events and unanticipated adverse device effects. Please note that adverse events are reportable to the IRB as UPIRSOs only if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the prompt reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented. In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified:

- *All Co-Investigators listed on the protocol.*
- *Yale IRB*
- *Independent Data Safety Monitoring Board*
- *Yale Investigational Drug Services*
- *National Institutes of Health*

The principal investigator and Victoria Greenberg, MD will conduct a review of all adverse events upon completion of every study subject. The principal investigator and Victoria Greenberg, MD will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

d. For multi-site studies for which the Yale PI serves as the lead investigator: N/A

13. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Our sample size calculation is based on a secondary analysis of a Maternal-Fetal Medicine Units (MFMU) randomized controlled trial and our own retrospective analysis of YNHH data. The secondary analysis analyzed a subset of women with stage 1 hypertension randomized to aspirin 60mg daily versus placebo. In this study, the incidence of stage 1 hypertension was 19%. The incidence of preeclampsia in women with stage 1 hypertension was 39% in total. There was a 40% decrease in relative risk of developing preeclampsia in women who took aspirin 60mg daily versus placebo.

A retrospective cohort study done at YNHH found a 29% incidence of hypertensive disorders of pregnancy in women with stage 1 hypertension. We anticipate a 40% risk reduction in the prevalence of preeclampsia from 29% in the placebo group to 18% in the aspirin group. To detect this difference with a power of 80% and □□ 0.05, we will need to randomize a total of 466 women with elevated blood pressure or stage 1 hypertension, 233 in each of the aspirin and placebo arms.

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

B. DRUGS/BIOLOGICS ☐N/A

1. If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1: The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:	
1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☒
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☒
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☒
2. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	☒
3. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☒

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

Low-dose aspirin is safe for use in pregnancy. Multiple large cohort and case-control studies have not found an association with congenital defects, structural, or developmental anomalies in the fetus. Several randomized controlled trials including thousands of women have demonstrated no increase in adverse fetal outcomes in doses less than 150mg per day.[1,3,6] A meta-analysis of 22 studies women demonstrated no increase in birth defects.[4]Use in the third trimester does not cause premature closure of the ductus arteriosus.[7]

Maternal use is safe without an increased risk of bleeding. There is no increased risk of gastrointestinal bleeding, placental abruption, epidural hematoma, and postpartum hemorrhage.[1] This was determined by several meta-analyses including over 20,000 pregnant women. [2]

Low dose aspirin is recommended for use during pregnancy to reduce risk of developing preeclampsia in women with at least one high risk factor or at least two moderate risk factors for developing preeclampsia. This management plan is recommended by numerous sources, including the United States Preventive Task Forces and the American College of Obstetricians and Gynecologists.[5] Aspirin will not be withheld from women who have indications for aspirin prophylaxis in pregnancy.

References:

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

1. CLASP Collaborative Group (1994). CLASP: a randomized trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. *Lancet, 343*(8898):619-629
2. Duley L, Henderson-Smart DJ, Meher S, & King JF (2007). Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Systematic Review*.
3. Golding J (1998). A randomized trial of low dose aspirin for primiparae in pregnancy: the Jamaica low dose aspirin study. *British Journal of Obstetrics and Gynecology, 105:*293-299
4. Kozer E et al (2002). Aspirin consumption during the first trimester of pregnancy and congenital anomalies: a meta-analysis. *American Journal of Obstetrics and Gynecology, 187*(6): 1623-1630
5. LeFevre ML, U.S. Preventive Services Task Force (2014). Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine, 161(11):819-826*
6. Pattison NS et al (2000). Does aspirin have a role in improving pregnancy outcome for women with the antiphoshoplipid syndrome? A randomized controlled trial. *American Journal of Obstetrics and Gynecology, 183:*1008-1012
7. Grab D, Paulus WE, Erdmann M, Terinde R, Oberhoffer R, Lang D, et al (2000). Effects of low-dose aspirin on uterine and fetal blood flow during pregnancy: results of a randomized, placebo-controlled, double-blind trial. *Ultrasound in Obstetrics and Gynecology,* 15: 19-27

3. Source: Identify the source of the drug or biologic to be used. *Write here*
Yale Investigational Drug Services will provide both the low dose aspirin and placebo.

a) Is the drug provided free of charge to subjects? ☒YES ☐NO
If yes, by whom? *Study investigator in conjunction with Yale Investigation Drug Services*

1. Storage, Preparation and Use: Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

Drug accountability:

Storage:

- *Aspirin is kept stored at room temperature (20-25 degrees Celsius). Study medications will be compounded by the Yale IDS. A weekly supply of pre-bottled medications will be stored at the Maternal-Fetal Medicine office located at 1 Long Wharf Drive, 2nd Floor, New Haven, CT. Temperature will be monitored continuously utilizing a NIST-approved temperature monitoring system. Patients will be dispensed once daily aspirin or placebo tablets monthly by our unblinded staff member Lauren Perley in accordance with the randomization scheme shared between herself and Yale IDS staff.*
- *Aspirin and placebo are individually encapsulated and packaged into childproof IDS bottles*

Preparation:

- *Study medication and placebo will be compounded and encapsulated by the Yale IDS*
- *Aspirin tablets will contain aspirin only and be encapsulated in cellulose*
- *Placebo will be cellulose only*
- *Aspirin and placebo tablets will be identical, as the aspirin will be encapsulated in cellulose to appear identical to the placebo tablets*

Stability:

- *Aspirin and placebo are stable at room temperature*
- *The aspirin and placebo tablets expire after 6 months. These expiration dates are clearly labeled and discussed with the patient.*

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

- *Unused study medication is collected at the completion of the study (after delivery of their baby) and returned to IDS*

Check applicable Investigational Drug Service utilized:

☒ YNHH IDS ☐ CMHC Pharmacy ☐ West Haven VA

☐ PET Center ☐ None

☐ Other:

Note: *If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.*

2. Use of Placebo: ☐Not applicable to this research project

If use of a placebo is planned, provide a justification which addresses the following:

a) Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.
No other available therapies.

b) State the maximum total length of time a participant may receive placebo while on the study.
Total length is from randomization until delivery (maximum 36 weeks). Aspirin will not be withheld from patients that would have otherwise received it as part of the standard of care were they not in this study. Women with any single high-risk factor or 2+ moderate risk factors will be offered aspirin as part of their clinical care and are not included in this study; this study only enrolls women with elevated blood pressure or stage 1 hypertension +/- only one other moderate risk factor.

c) Address the greatest potential harm that may come to a participant as a result of receiving placebo.
Greatest harm would be hypersensitivity to any included ingredient in the placebo

d) Describe the procedures that are in place to safeguard participants receiving placebo.
Use of Yale IDS for preparation of placebo
Data Safety Monitoring Committee will review both the aspirin and placebo arms for any adverse events

3. Continuation of Drug Therapy After Study Closure ☒Not applicable to this project

Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access. *Write here*

☒ NO If no, explain why this is acceptable.
Use of low dose aspirin is beneficial during pregnancy to reduce the risk of preeclampsia. The American College of Obstetricians and Gynecologists does not currently endorse postpartum use.

B. DEVICES ☒N/A

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol: *466*
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: *N/A*

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☐ Flyers	☐ Internet/web postings	☐ Radio
☒ Posters	☐ Mass email solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☒ Medical record review*	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☒ Clinicaltrails.gov
☐ YCCI Recruitment database	☐ Social Media (Twitter/Facebook):	
☐ Other:		

* Requests for medical records should be made through JDAT as described at
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.
Subjects will be identified through routine prenatal visits at Yale-associated OBGYN offices (maternal-fetal medicine office, Women's Center, Yale Health Plan, and private obstetric offices that deliver at YNHH). Blood pressures will be observed for the year preceding pregnancy and up to 20 weeks gestation through chart review.

b. Describe how potential subjects are contacted.
Subjects will be contacted in person during the time of a routine prenatal visit.

c. Who is recruiting potential subjects?
All research staff personnel. Potential subjects may also be referred to research staff by clinical staff at the above-mentioned clinic locations.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects
☒Yes, some of the subjects
☐No

If yes, describe the nature of this relationship.
Primary investigator may be the physician in charge of care for a subset of these women, if they are recruited from the maternal-fetal medicine office or present to labor and delivery at Yale's York Street campus.

5. **Request for waiver of HIPAA authorization:** (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study
☒ For recruitment/screening purposes only
☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: *We will need to review the potential subject's medical record prior to approaching her about the*

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

study in order to confirm that she is medically eligible. It is impractical to approach patients about the study if they are not medically eligible, given the time involved in approaching patients and the volume of patients seen at the clinics. Once we have determined initial medical eligibility, we will then screen those patients in-person to confirm all eligibility criteria has been met.

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: N/A

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.
   The entire consent form will be reviewed with interested women who meet study inclusion criteria and do not have any exclusion criteria. The consent form will be summarized verbally by research staff personnel, with time for questions at each section of the consent form. Women will then be asked to read the consent form. Any questions or concerns will be reviewed. Women ages 18+ will be enrolled, so parental permission is not required. Women will only be included if they are English or Spanish-speaking. If another person is with the woman during her routine prenatal visit, she will be asked if she would like to discuss the study on her own or together with the accompanying person or people.

   The consent form has been translated into Spanish by the Yale Center for Clinical Investigation's translation services. Spanish-speaking patients will be consented by utilizing Yale language services.

7. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.
   Women will be assumed to have capacity to provide informed consent for research unless there is indication to the contrary. These indications include: known cognitive impairment, altered mental status, difficulties in communication observed during research staff interaction, psychotic symptoms, bizarre behavior. Women with these indications will not be included in the research study. If any of these symptoms or behaviors are new, their medical provider will be informed immediately for further assessment.

8. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.
   Spanish speakers will be included. The consent form has been translated by the Yale Center for Clinical Investigation's official translation services. Spanish speaking participants will be counseled utilizing Yale language services for all discussions and study visits.

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☒Not Requesting any consent waivers

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?
    - Past medical and surgical history, allergies, family history
    - Medication list
    - The rest of the participant's medical record held by Yale New Haven Health created from the start of pregnancy and up to 1 year after delivery
    - Records about phone calls made as part of this research
    - Records about study visits
    - Information obtained during this research regarding
        - Vital signs, in including blood pressure
        - Physical exams
        - Laboratory, x-ray, and other test results
        - Diaries and questionnaires
        - The diagnosis and treatment of any physical or mental health condition
        - Records about any study drug received
    - Neonatal and infant records until 1 year of age
        - Information obtained during this research regarding
            - Birthweight
            - Apgar scores
            - Delivery records
            - Laboratory, x-ray, and other test results

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

- Diagnosis and treatment of any physical or mental health condition
- Outpatient, emergency department, and hospital visits/admissions until 1 year of age

2. How will the research data be collected, recorded and stored?

Data will be collected from the patients' medical records (including the medical record of their baby) and from self-report. It will be recorded/stored in REDCap, OnCore and on a Yale server accessible only to members of the research team. This server is on a secure, encrypted hospital-issued computer.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☐ Laptop Computer ☒Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

All subjects will be assigned a unique study ID code upon enrollment. Documents linking the patient to their ID code will be kept on a Yale server accessible only to members of the research team. This server is on a secure, encrypted hospital-issued computer. All data will be de-identified at the conclusion of chart review. Data analysts will have access to only de-identified information. Patient consent forms and chart abstraction forms will be kept in a locked cabinet in a locked research office at the Yale Maternal-Fetal Medicine office. This locked cabinet may only be accessed by research personnel.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

Data will remain on an encrypted server through Yale University. If research personnel leave the university, data will not travel with them.

6. If appropriate, has a Certificate of Confidentiality been obtained?

N/A

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

There may be reduction in rates of hypertensive disorders of pregnancy (gestational hypertension, preeclampsia, HELLP syndrome, eclampsia) both to study participants and future pregnant women with elevated BP and stage 1 hypertension.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

If women do not want to participate in the study, they will continue routine prenatal care.

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

2. Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   N/A

3. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   There are no costs to study participants. Study medications (whether low dose aspirin or placebo) will be provided at no cost. No further interventions or procedures will be required.

4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

   a. Will medical treatment be available if research-related injury occurs?

      Medical treatment will not be available from research staff.

   b. Where and from whom may treatment be obtained?

      Medical treatment will be through the participant's usual provider, emergency room, and any other health professionals as needed.

   c. Are there any limits to the treatment being provided?

      No.

   d. Who will pay for this treatment?

      Insurance will be billed for any treatment and the participants will be responsible for any co-pays required by the insurance company for standard treatment.

   e. How will the medical treatment be accessed by subjects?

      If needed, medical treatment will be sought through usual avenues—either through the patient's usual healthcare provider (whether obstetrician or primary care physician) or emergency department. Participants will be asked to report any side effects of study medication (whether aspirin or placebo). If any side effects are reported, research personnel will encourage and help set up medical diagnosis and treatment services.

      During the study visits (whether conducted in person or by telephone), we will ask women questions about their blood pressure and symptoms of preeclampsia. If any study participant notes onset of preeclampsia symptoms (headache, vision changes, right upper quadrant pain, and/or dyspnea) or new onset of systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, she will be asked to contact her primary obstetrician immediately.

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☒ No☐

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities?
Yes ☒ No ☐

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the specific procedure that you will perform? Yes ☒ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☒

c. Will a novel approach using existing equipment be applied? Yes ☐ No ☒

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.

APPROVED BY THE YALE UNIVERSITY IRB 12/8/2021