PROSPECTIVE PROTOCOL TEMPLATE

INSTRUCTIONS:

- *This protocol template should be used for investigator-initiated PROSPECTIVE biomedical or behavioral research. For retrospective studies, use the* ***Retrospective Protocol Template.docx*** *document.*
- *WIH IRB policy requires that protocols are at least 2-3 pages and provide an "expanded description of the project."*
- *Remove all instructions in italics (including these) so that they are not contained in the final version of your protocol.*
- ***IMPORTANT****: Be sure that the protocol is consistent with information provided in the CNE Research Application, Consent, and all other study materials.*

STUDY TITLE: Implementing an app-based remote blood pressure monitoring program to reduce health disparities among women with hypertension during pregnancy

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1. OBJECTIVES, SPECIFIC AIMS, BACKGROUND, AND SIGNIFICANCE

Preeclampsia or gestational hypertension—described as hypertension in pregnancy—affects up to 10% of all pregnancies and is a main driver of maternal morbidity in Rhode Island and the United States.[1-14] The rates of hypertension in pregnancy have disproportionately affected women of color and may explain why racial minorities have higher maternal morbidity.[1,12] The American College of Obstetricians and Gynecologists has called for novel interventions to improve health equity and maternal morbidity outcomes among women hypertension in pregnancy. Technology-based interventions (i.e. remote blood pressure monitoring, telehealth visits, text-based communication) have improved access to care but, to date, have not yet demonstrated an effect on reducing maternal morbidity outcomes.[15-17] It is possible that the lack of effect on maternal morbidity is due to the simplicity of the technology-based interventions previously employed (i.e. text message-based systems). Advanced digital health interventions on blood pressure--namely remote blood pressure monitoring through Bluetooth-enabled blood pressure cuffs and incorporation of a commercially available smartphone application that includes education and patient support as part of a "hypertension in pregnancy pathway"—may more effectively improve perinatal health equity compared to standard SMS-based messaging by reducing perinatal morbidity/mortality among women of color hypertension during their pregnancy. We propose a *pilot randomized control trial* to examine the feasibility, acceptability, and preliminary estimates of effects of smartphone application-based (app-based) Bluetooth enabled remote blood pressure monitoring (intervention group) when compared to a SMS (short message system such as text message) based remote blood pressure monitoring group (control group). Our *long-term goal* is to use the most cost-effective intervention (app-based vs SMS-based remote blood pressure monitoring) to improve health equity and maternal morbidity outcomes for pregnant women with hypertension during pregnancy who live in Rhode Island and beyond. We plan to use pilot data from this proposal to support an efficacy trial powered to detect differences in maternal morbidity outcomes between app-based remote blood pressure monitoring and routine care with SMS monitoring.

In addition, this proposal stems from a hospital-wide effort at Women & Infants Hospital (WIH) to reduce racial disparities among women of color in terms of frequency of severe maternal morbidity (SMM). SMM is a metric created by the Centers for Disease Control and Prevention that includes blood transfusion as well as adverse outcomes ranging from arrhythmia to eclampsia to intubation. SMM associated with hypertension is driven by asymptomatic postpartum hypertension. This is easily identified and managed prior to becoming SMM when patients adhere to recommended blood pressure checks after discharge. Excluding blood transfusion (which does not pertain to hypertension), the overall rate of SMM among women with hypertension during pregnancy who deliver at WIH is 6.6%. However, there is a significant difference along racial and ethnic lines: the rate of SMM in the setting of hypertension among black women is 6.8% compared to 4.5% among white women, and the rate of SMM in the setting of preeclampsia is 9.4% among Hispanic women compared to 4.9% among non-Hispanic women. The overall dual aim of the initiative is to reduce the disparity in rates of SMM among those with hypertension between black and white women and between Hispanic and non-Hispanic women by at least 33% by December 31, 2022. *As part of WIH's equity initiative, automatic blood pressure cuffs (non Bluetooth enabled) will be provided to all women with hypertension at discharge from delivery hospitalization as part of*

routine care. We plan to compare rates of SMM before versus after the hospital-wide implementation of SMS-based remote blood pressure monitoring. Thus, for this proposal, we will build the foundation for our long-term goal and for hospital-wide equity projects by exploring whether app-based remote blood pressure monitoring is required to decrease maternal morbidity compared to standard care with remote SMS blood pressure monitoring.

For this pilot study, sample size limitations will require the use of surrogate markers of maternal morbidity to serve as patient outcomes, which have been selected based on evidence-based best-practices.[1-14] The primary clinical outcome for this study will be blood pressure measurement obtained three to ten days postpartum. Prespecified secondary outcomes include *postpartum readmission for blood pressure management* (e.g. rehospitalizations within 30 days of discharge), *adherence to evidence-based best-practices* (e.g. medications, antepartum surveillance, blood pressure ascertainment, postpartum blood pressure goal of <140/90), *composite severe maternal morbidity* (i.e. stroke, seizure/eclampsia, posterior reversible encephalopathy syndrome, pulmonary edema, heart failure, myocardial infarction, acute fatty liver of pregnancy, hemolysis, elevated liver enzymes and low platelets, placental abruption, post-partum hemorrhage, blood transfusion, acute kidney injury, and transaminitis), *postpartum maternal mortality*, and *composite neonatal morbidity* (i.e. umbilical artery pH <7.10, umbilical artery lactate, seizures, therapeutic hypothermia, hypoxic-ischemic encephalopathy, mechanical ventilation, intrauterine fetal death, neonatal death). We will also explore patient preferences as to treatment group via the Agency for Healthcare Research and Quality Consumer Assessment of Healthcare Providers and Systems (AHRQ CAHPS) survey and compared between both intervention groups and standard prenatal care.[25] CAHPS survey will provide mixed quantitative and qualitative assessments. Our *central hypothesis* is that app-based Bluetooth enabled blood pressure monitoring will improve adherence to evidence-based best practices and will demonstrate signals towards improved health equity and maternal morbidity outcomes compared to SMS-based remote blood pressure monitoring.

2. STUDY DESIGN, METHODS, AND PROCEDURES

Study Design

2.1 Study Design**:** We will conduct a *pilot randomized control trial* of **120** women who deliver at Women and Infant's Hospital of Rhode Island (WIHRI) and plan to receive postpartum care at a WIHRI-affiliated clinic. We will use broad inclusion criteria and analyze data using the intention-to-treat principle to increase generalizability of the findings.

2.2 Eligibility criteria: Inclusion criteria: a) English- or Spanish-speaking b) maternal age ≥18 years old, c) smartphone ownership for remote blood pressure ascertainment, d) diagnosis of gestational hypertension, preeclampsia, or chronic hypertension, e) plan to receive postpartum care at a Women & Infants Hospital (WIH)-affiliated clinic. Exclusion criteria: a) fetal anomaly, b) prisoners, c) lack of smartphone, and d) inability to consent.

2.3 Screening, consent, and recruitment: Eligible women will be recruited at the Women and Infant's Hospital of Rhode Island (WIHRI) 's obstetrics units (obstetric triage, labor & delivery, antepartum care unit, and postpartum care unit) during their delivery hospitalization. Recruitment will be conducted by a research assistant or study principal investigator or co-investigator.

2.4 Randomization and blinding: Regardless of when their diagnosis of chronic hypertension, gestational hypertension, or preeclampsia with or without features occurs before or during delivery hospitalization, upon hospital discharge all patients will receive an automatic blood pressure cuff from WIHRI if their insurance does not cover this (or if they do not have one already); for patients whose insurance does cover automatic blood pressure cuffs, the provider will provide them with a prescription for this device at time of diagnosis. This is part of WIHRI's equity initiative related to hypertension: as stated previously, WIHRI has committed to provide non-Bluetooth enabled blood pressure cuffs to all eligible patients.

Those who consent to participate in the study, complete baseline study surveys, and receive a blood pressure cuff prior to discharge will be randomized 1:1 via a computer-generated randomization sequence to one of two protocols: *app based remote blood pressure monitoring* (intervention group) or and standard PNC with SMS-based monitoring (comparison group). The study staff will remain blinded to intervention, except for the research assistant who will be, by necessity, unblinded.

They will receive the following per their randomization group:

Standard care (comparison group)

All women will receive education and counseling from their physician providers on evidence-based best-practices and red-flags for pregnancy's complicated by chronic hypertension, preeclampsia, or gestational hypertension. They will participate in WIHRI's ongoing equity initiative using automatic blood pressure cuffs in a remote hypertension monitoring program supported by a nurse practitioner and community health worker.

App-based remote blood pressure monitoring (intervention group)

Women in this group will receive a Bluetooth-enabled automatic blood pressure cuff that sends messages through an affiliated smartphone application to providers upon recording each measurement. This affiliated smartphone application will also contain education on hypertension management. Upon receipt of the blood pressure cuff, participants will be instructed to set up the program/app such that the research assistant (RA) will receive all recorded blood pressure managements. All patients will receive instructions on how to obtain blood pressure and will be instructed to call their on-call provider if the blood pressure is >160/110 mmHg. The RA will review each patient's blood pressure log daily to ensure blood pressures remain mild-range (i.e. 140-159/90-109 mmHg) or less.

2.5 Study procedures: Perinatal data will be collected and directly entered by the research assistant or principal investigators into REDCap, a secure database hosted by WIHRI. Data will be collected on a rolling basis to ensure timely collection and monitoring for unseen adverse events.

Potential challenges and alternative approaches: Obtaining our target sample size may be challenging due to the incidence of hypertension diseases of pregnancy in the literature. However, we anticipate having a sufficient population from which to recruit for this pilot study given the 18 month study period and the relatively small sample study. However, should our target sample size be lower than expected, we may expand recruitment into private practice groups who have separate admitting privileges.

Since starting recruitment, an additional challenge has developed: up to 10% of participants in the equity program (who may or may not be in the study) are discharged without blood pressure cuffs with the plan for a home visit to provide a BP cuff within 3-7 days after discharge. In addition, about 10% of patients who participated in the study did not complete their baseline study survey. To ensure we obtain a study population of 120 who follow the study protocol, we have developed an alternative approach by changing our inclusion criteria. Specifically, eligible people may be consented and randomized but only those who receive a BP cuff *and* complete their intake survey prior to discharge will be included in the trial's analytic population. We anticipate needed to randomize up to 160 patients in order to obtain our desired study population of 120 participants.

2.6 Study outcomes and Power:

Primary outcome: The primary outcomes will be adherence to recommended blood pressure check 3-10 days postpartum, as is recommended per standard of care. Our sample size of **120** pregnant women with gestational hypertension or preeclampsia will allow us to detect a 60% increase in adherence to recommended blood pressure check from the baseline rate of 50%, using a two-tailed alpha of 0.05. The 60% improvement (i.e. from 50% to 80% adherence) is conservative as it is less than has been reported in the medical literature.[15-17] *Secondary outcomes*: Secondary outcomes will be surrogate markers of maternal morbidity. Prespecified secondary outcomes include *postpartum readmission for blood pressure management* (e.g. hospital admission for blood pressure management within 30 days of discharge), *adherence to evidence-based best-practices* (e.g. medications, blood pressure ascertainment, postpartum blood pressure goal of <140/90), *composite severe maternal morbidity* (**Table 2**), and *composite neonatal morbidity* (Table 1). Our study will likely not be powered to detect differences in secondary outcomes due to the rarity of the individual patient outcomes but will provide us crucial pilot data for the subsequent study.

We will also explore patient preferences as to treatment group via the Agency for Healthcare Research and Quality Consumer Assessment of Healthcare Providers and Systems (AHRQ CAHPS) survey and compared between both intervention groups and standard prenatal care.[25] Per AHRQ guidelines, 100 CAHPS surveys must be completed in a pilot study to determine a difference in patient experience between care models.[25] Our study population of **60 women** per group (120 women total) is anticipated to generate ~100 completed surveys per group (200 total), based on an anticipated response rate of 80% and each participant completing two surveys. Upon enrollment, participants will choose whether they desire to complete the AHRQ CAHPS surveys in paper, online through email, or via a text-message platform; regardless of route, surveys will be collected at randomization and at ~30-45 days postpartum. On the second survey, participants will also complete a validated scale, the Decision Regret Scale.[26] Of note, both the AHRQ CAHPS study and the Decision Regret Study are already validated in Spanish.

Table 2. Composite maternal and neonatal morbidity outcomes

Composite maternal morbidity
Stroke
Seizure/eclampsia
Acute fatty liver of pregnancy
Posterior reversible encephalopathy syndrome
Pulmonary edema
Heart failure
Hemolysis elevated liver enzymes and low platelets
Placental abruption
Post-partum hemorrhage
Acute kidney injury
Transaminitis
Composite neonatal morbidity
Umbilical artery pH < 7.10
Umbilical artery lactate
Seizures
Therapeutic hypothermia
Hypoxic-ischemic encephalopathy
Mechanical ventilation (i.e. intubation)
Supplemental oxygen 0-6 hours, 6-12 hours, 12-24 hours, >24 hours of life
Intrauterine fetal death
Neonatal death

2.6 Data Management, Sources of Materials, Records/Data to be reviewed: Antepartum, maternal/neonatal, pregnancy, and perinatal data will be collected and directly entered by the research assistant or principal investigator into REDCap, a secure database hosted by WIHRI. All primary and secondary outcomes will entered into REDCap by the RA or study team. Thus, the data to be reviewed will only be collected by key study personnel. In addition, pregnancy characteristics (maternal weight, disease comorbidities, etc.) and demographic information (reported race/ethnicity, insurance type, zip code) will be collected post-delivery and entered into REDCap. Prior to data analysis, all patient identifiable information will be stripped to ensure patient confidentiality. Our REDCap database will be encrypted by multiple levels of password protection (accessing computer, network, and logging into database) that will only be accessible by key research personell. Anti-virus software is installed and up to date and the operating system is up to date with all Windows and Apple updates.

Material/Specimen Management: No specimens will be stored outside of standard care (such as umbilical cord gases processed by laboratory per usual clinical protocol).

Provisions to monitor the data to ensure the safety of subjects: Our study does not involve greater than minimal risk. However, we will monitor for unanticipated adverse outcomes. As a part of this, key study personnel (Drs. Polnaszek, Lewkowitz) will monitor for adverse outcomes on a weekly basis. Should any unanticipated outcomes be found, this will be reported back to the IRB. Beyond the weekly monitoring of patients/data, this will also be performed globally on a quarterly basis.

Withdrawal of subjects: Patients will not be withdrawn from the study.

2.7 Data analysis: Analysis will follow the intention-to-treat principle. Continuous variables will be compared using the Student's *t*-test or Mann Whitney *U* test, as appropriate. Categorical variables will be compared using the χ^2 or Fisher's exact test, as appropriate. We will calculate crude and unadjusted risk ratios and differences. We will use multivariable logistic regression to adjust for potential confounders. Qualitative data obtained from CAHPS survey will also be analyzed using Nvivo, a computer-assisted qualitative data analysis software provided by Brown University. This software promotes inquiry beyond coding, sorting and retrieval of data. It is designed to integrate coding with qualitative linking, shaping, and modeling that may inform health equitable care. Dr. Lewkowitz and Polnaszek have used Nvivo softward. In addition, Dr. Polnaszek has utilized this procedure to capture qualitative data previously to successfully design, implement, and launch a new model of health care for vulnerable patients transitioning from the hospital to sub-acute care facilities.[27]

2.8 Plan to include a diverse population

Inclusion of minorities: This proposal aims to reduce health inequity among women of color with gestational hypertension, preeclampsia, or chronic hypertension. Rates of hypertensive disease in pregnancy are higher among minority women. Given this is our target population, we anticipate that a significant proportion of women included in our study will be minorities. Recruitment will be conducted at prenatal clinics by a research assistant or member of the study team.

Inclusion of fetuses, neonates, and pregnant women: Recent data suggests utilizing remote blood pressure monitoring via text messaging and automatic blood pressure cuffs improves adherence to recommended care.[15-17] As this practice should become standard of care, WIHRI plans to implement SMS-based remote blood pressure monitoring hospital wide for all eligible patients. However, the effect of SMS-based messaging on reducing maternal morbidity outcomes pertaining to hypertension is unknown. In this pilot study, we will compare standard of care (SMS-based remote blood pressure monitoring) to a high quality digital health intervention (smartphone app provided patient education and linked Bluetooth-enabled blood pressure monitoring). This innovative study will allow us to obtain pilot data to determine whether additional digital health support (Bluetooth enabled cuff and app-provided education) is more effective at improve health equity among women of color who deliver at WIH when compared to standard care (SMS-based remote blood pressure monitoring).

3.9 Participant Reimbursement: No reimbursement will be provided for participation, but all participants who complete all required surveys will be entered into a raffle with a prize of $100

3. REFERENCES

1. Bulletins—Obstetrics ACoOaGCoP. ACOG Practice Bulletin No. 203: Chronic Hypertension in Pregnancy. *Obstet Gynecol.* 2019;133(1):e26-e50.
2. Seely EW, Ecker J. Chronic hypertension in pregnancy. *Circulation.* 2014;129(11):1254-1261.
3. Fox A, McHugh S, Browne J, et al. Estimating the Cost of Preeclampsia in the Healthcare System: Cross-Sectional Study Using Data From SCOPE Study (Screening for Pregnancy End Points). *Hypertension.* 2017;70(6):1243-1249.
4. Prevention CfDCa. Core state preconception health indicators — Pregnancy Risk Assessment Monitoring System and Behavioral Risk Factor Surveillance System, 2009. In.
5. Prevention. CfDCa. Morbidity and Mortality Weekly Report, November 22, 2013. "CDC health disparities and inequalities report — United States, 2013. In.
6. Bryant AS, Worjoloh A, Caughey AB, Washington AE. Racial/ethnic disparities in obstetric outcomes and care: prevalence and determinants. *Am J Obstet Gynecol.* 2010;202(4):335-343.
7. Naeye RL. Causes of perinatal mortality in the US Collaborative Perinatal Project. *JAMA.* 1977;238(3):228-229.
8. Prevention. CfDCa. Pregnancy Mortality Surveillance System. January 2017. . In.
9. Prevention. CfDCa. Infant mortality statistics from the 2013 period linked birth/infant death data set. In.
10. Alhusen JL, Bower, K.M, Epstein, E., & Sharps, P. Racial discrimination and adverse birth outcomes: an integrative review. In:2016.
11. Foundation KF. Beyond health care: the role of social determinants in promoting health and health equity. In:2015.
12. Sharma G, Ying W, Vaught AJ. Understanding the Rural and Racial Disparities in Pre-Pregnancy Hypertension: Important Considerations in Maternal Health Equity. *J Am Coll Cardiol.* 2020;76(22):2620-2622.
13. Azzopardi D, Wyatt JS, Cady EB, et al. Prognosis of newborn infants with hypoxic-ischemic brain injury assessed by phosphorus magnetic resonance spectroscopy. *Pediatr Res.* 1989;25(5):445-451.
14. Vedam S SK, MacDorman M, Declercq E, Cramer R, Cheyney M, et al. Mapping integration of midwives across the United States: Impact on access, equity, and outcomes. In. PLoS ONE 13(2): e0192523. **2018**.
15. Hoppe KK, Thomas N, Zernick M, et al. Telehealth with remote blood pressure monitoring compared with standard care for postpartum hypertension. *Am J Obstet Gynecol.* 2020;223(4):585-588.
16. Hirshberg AM, Katy. Srinivas, Sindhu. Heart Safe Motherhood: Applying Innovation Methodology for Improved Maternal Outcomes. In. New England Journal of Medicine2019.
17. Mukhtarova N, Alagoz O, Chen YH, Hoppe K. Evaluation of different blood pressure assessment strategies and cutoff values to predict postpartum hypertension-related readmissions: a retrospective cohort study. *Am J Obstet Gynecol MFM.* 2021;3(1):100252.
18. Reese RL, Clement SA, Syeda S, et al. Coordinated-Transitional Care for Veterans with Heart Failure and Chronic Lung Disease. *J Am Geriatr Soc.* 2019;67(7):1502-1507.
19. McKenney KM, Martinez NG, Yee LM. Patient navigation across the spectrum of women's health care in the United States. *Am J Obstet Gynecol.* 2018;218(3):280-286.

20. Shommu NS, Ahmed S, Rumana N, Barron GR, McBrien KA, Turin TC. What is the scope of improving immigrant and ethnic minority healthcare using community navigators: A systematic scoping review. *Int J Equity Health.* 2016;15:6.
21. Wang ML, Gallivan L, Lemon SC, et al. Navigating to health: Evaluation of a community health center patient navigation program. *Prev Med Rep.* 2015;2:664-668.
22. Fisher NDL, Fera LE, Dunning JR, et al. Development of an entirely remote, non-physician led hypertension management program. *Clin Cardiol.* 2019;42(2):285-291.
23. Yatabe J, Yatabe MS, Ichihara A. The current state and future of internet technology-based hypertension management in Japan. *Hypertens Res.* 2021;44(3):276-285.
24. Post DM, McAlearney AS, Young GS, Krok-Schoen JL, Plascak JJ, Paskett ED. Effects of Patient Navigation on Patient Satisfaction Outcomes. *J Cancer Educ.* 2015;30(4):728-735.
25. Quality AfHRa. Consumer Assessment of Healthcare Providers and Systems. https://www.ahrq.gov/cahps/about-cahps/index.html. Published 2021. Accessed 10/21/21, 2021.
26. Brehaut JC, O'Connor AM, Wood TJ, Hack TF, Siminoff L, Gordon E, Feldman-Stewart D. Validation of a decision regret scale. Med Decis Making. 2003 Jul-Aug;23(4):281-92
27. King BJ, Gilmore-Bykovskyi AL, Roiland RA, Polnaszek BE, Bowers BJ, Kind AJ. The consequences of poor communication during transitions from hospital to skilled nursing facility: a qualitative study. *J Am Geriatr Soc.* 2013;61(7):1095-1102.