Detailed Protocol

Heart Health 4 Moms: Disease Prevention in Women with a Recent History of Pregnancy Complications

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BACKGROUND AND SIGNIFICANCE

In their lifetime, 4-8% of the 85 million American mothers alive today will have at least one pregnancy complicated by preeclampsia, a hypertensive disorder characterized by new onset hypertension during the second part of pregnancy with elevated urine protein (Ness; Cunningham, 2009). Although most women with preeclampsia return to normal blood pressure after delivery, they are at four times the risk of developing chronic hypertension and two times the risk of cardiovascular disease (CVD) in the years following pregnancy, even in the early years after pregnancy, but extending at least until early menopause (Bellamy, 2007; McDonald, 2008; Brown, 2013). Based on the link between preeclampsia and CVD, the American Heart Association (AHA) recommended for the first time in 2011 that clinicians consider a history of preeclampsia as a risk factor for CVD (Mosca, 2011). The AHA recommended that obstetricians refer women with a history of preeclampsia to primary care physicians or cardiologists so lifestyle modifications, screening and timely treatment could be implemented. However, in reality, our health care system is disjointed, leaving a large gap between obstetric and primary care. Many young women do not avail themselves of health care services outside of pregnancy (What women want, AAFP Press release, 2008). In addition, it is typical for women with preeclampsia to be counseled that their health will return to "normal" after delivery, meaning that they are not aware that they are at an increased risk of CVD later in life, much less how to reduce that risk. Even women who have relationships with primary care providers may not receive the suggested care as primary care physicians may be unaware of the patient's detailed obstetric record and thus, their history of preeclampsia. The postpartum period has been identified as a 'window of opportunity' for behavior change given the recency of the complicated pregnancy and new motivation to take of one's health in the context of being a new mother (Rich-Edwards, 2010; Bentley-Lewis, 2008; Beckles, 2001). However, the postpartum first year is an especially difficult one for mothers to reach the clinic and other programs outside the home. In response to this, we built and tested a successful internet-based lifestyle modification program for patients with a recent history of gestational diabetes mellitus (Balance After Baby, #2009P002118) to help them reduce their weight in the first year of post-partum (Nicklas, 2014). The success of this intervention has led us to develop and test a similar program for women with a history of preeclampsia.

This project is a randomized trial of a lifestyle modification program for women with recent preeclampsia designed to educate them about their elevated CVD risk and how to reduce that risk, as well as instilling confidence in their ability to make or maintain heart healthy changes in their lifestyle. This program will consider **both the opportunities and challenges for postpartum women**, including the **competing demands of personal self-care versus care**

of the family, fatigue and exhaustion, and the specificities of caloric requirements of breastfeeding when pursued in an effort of caloric reduction (Nicklas, 2011; Nicklas 2012). The Patient Centered Outcomes Research Institute funds this project. This study is being run in collaboration with the Preeclampsia Foundation.

I. SPECIFIC AIMS

Aim 1: ***Improve patient ratings of their self-efficacy*** to achieve a healthy lifestyle through healthy eating and increased physical activity;

Aim 2***:*** ***Improve patient behavioral risk factors***: Increase adherence to the Dietary Approaches to Stop Hypertension (DASH) diet, increase physical activity, and reduce physical inactivity;

Aim 3**:** Improve patient ratings of their ***self-efficacy to promote healthy lifestyle for their family***, an exploratory element that patients have identified as important;

Aim 4: Improve ***patient knowledge of CVD risk*** and risk prevention options after preeclampsia;

Aim 5 (secondary aims): Test the extent to which the program will improve clinical risk factors for CVD at 3 and 9 months after baseline, including:

a. Lower postpartum weight retention
b. Lower postpartum blood pressure

SUBJECT SELECTION

a. Inclusion criteria

1) Healthy female currently pregnant (subjects will not be studied until postpartum but can be recruited during pregnancy) or before 5 years and 1 month of a delivery with a live birth complicated by preeclampsia per the following definition from the International Society for the Study of Hypertension in Pregnancy (Brown, 2001, see table below) and confirmed by medical record review:

Blood pressure	• Greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks gestation in a woman with a previously normal blood pressure* OR • Greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic once AND diagnosis of preeclampsia
AND	
Proteinuria	• Greater than or equal to 300 mg per 24 hour urine collection (or this amount extrapolated from a timed collection) OR • Urine protein/creatinine ratio greater than or equal to 0.3* OR • Dipstick reading of 1+ (used only if other quantitative methods not available) *Each measured as mg/dL

*Normal blood pressure will be defined as follows:

MENTION OF:

normotension or normal pregnancy

OR

At least one measure of less than or equal to 140 mm Hg systolic or less than or equal to 90 mm Hg diastolic

AND NONE OF THE FOLLOWING:

More than ONE measure with SBP≥140 and/or DB≥90 mmHg

Mention of chronic hypertension or high blood pressure

Anti-hypertensive medication before diagnosis of PE

2) Age ≥ 18 years and < 45 years.
3) Access to the internet via Internet enabled mobile devices that use either iOS or Android operating systems;
4) Post-partum body mass index between 18.5 and 40 kg/m^2 (based on the WHO definition underweight and of morbid obesity or grade III obesity)) and weight ≤350 lbs;
5) Normal postpartum blood pressure (<140/90 mmHg) (average of the 4 readings done at home, as described in the following section) while not on antihypertensive medication;
6) Capable of communicating in English or Spanish at a 8^{th} grade level;
7) Capable of providing informed consent.

b. Exclusion criteria

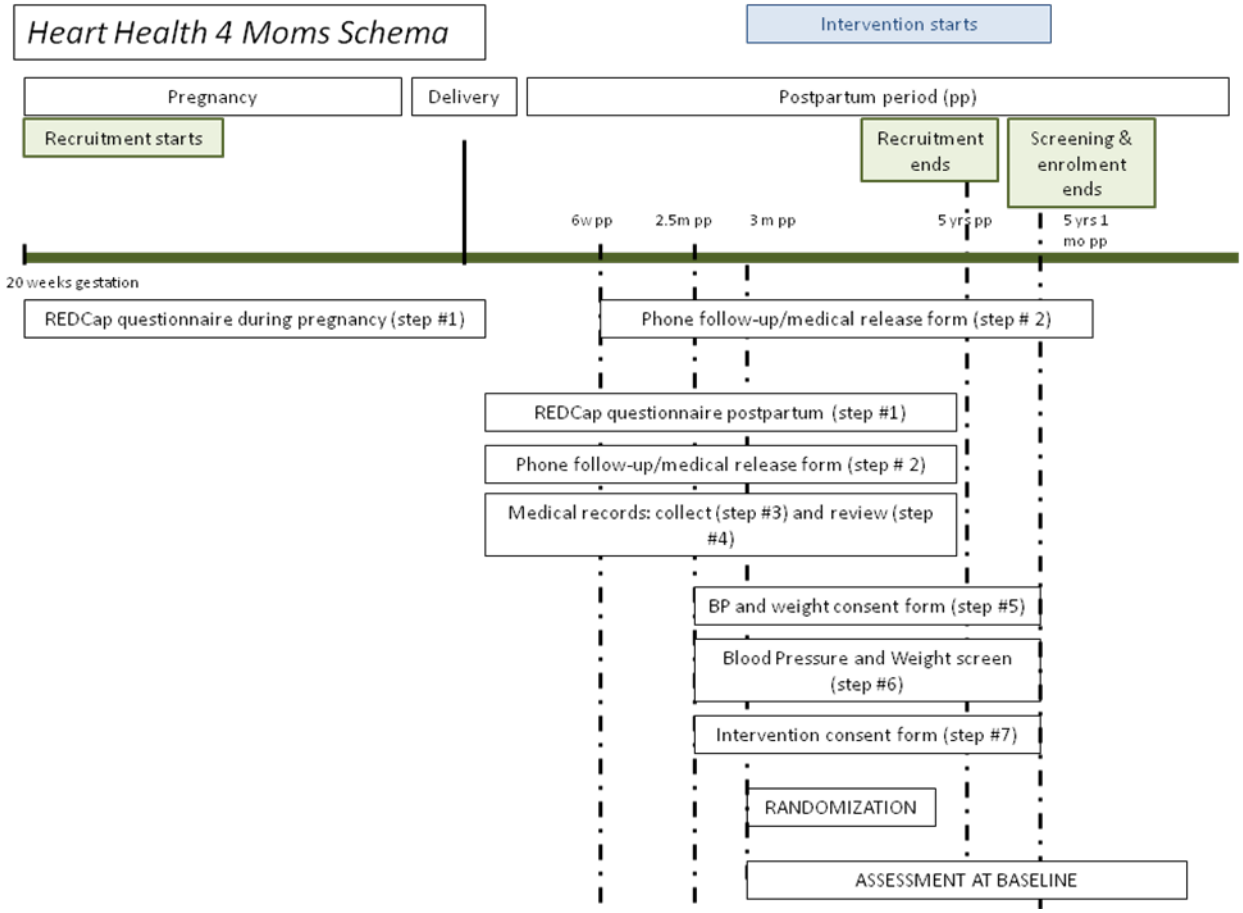
1) Baby not living at home at time of enrollment;
2) Diagnosis of diabetes (type 1, 2, or a secondary form of diabetes);
3) Current addiction or abuse of any type (alcohol or drugs) at time of recruitment;
4) Taking prescription medication associated with weight gain (such as atypical antipsychotics, respirdal (respiradone), clozapine (klozaril), olanzapine (zyprexa), quetiapine (seroquel), etc.) at randomization;
5) Active self-reported eating disorder such as anorexia, bulimia or binge eating;
6) Active treatment for cancer;
7) Personal history of heart disease, stroke or kidney disease;
8) Personal history of gastric bypass or bowel surgery resulting in malabsorption;
9) Active medical problem that would interfere with the following of the diet or changes in blood pressure and/or weight;

c. Source of subjects and recruitment methods

We will recruit 151 women through online postings, and flyers, through the Preeclampsia Foundation and its various media venues, as well as Craigslist, Babycenter.com, other internet websites and through the 2,800 community health clinics affiliated with the National Association of County and City Health officials (NACCHO, a partner in this grant) or other community centers. Advertisements for the study as well as the entire program are available in English and in Spanish (documents submitted).

Ellen Seely, MD (Principal Investigator) and Janet Rich-Edwards, ScD (Principal Investigator) will oversee the recruitment process. The study staff (please see accompanying CITI completion certificates for study staff) has completed training in the protection of human research participants. Participants and study staff will communicate via the mode chosen by participants: phone calls, video calling such as Skype (including chat), texts or other throughout the study. Consent form will be sent only by regular mail, as explained in Step #6 of the subject enrollment plan.

SUBJECT ENROLLMENT



d. Methods of enrollment

Step #1: Preliminary eligibility screen by brief REDCap questionnaire

As we are expecting a high volume of responses to our several recruitment sources, a first step screening will be done through a REDCap questionnaire (submitted), for which the subject will find a link on a web advertisement or on a flyer as well as the Research assistant' s phone number and email address. This questionnaire will serve as an eligibility screen to ascertain that subjects self-report a preeclamptic pregnancy, are

within the enrollment window, and are living in the US or territories. Subjects will remain eligible to proceed as long as they have completed the Recruitment Questionnaire before 5 years postpartum. The data from this REDCap survey will be maintained as non-identified data to allow us to describe the source population for our study.

Subjects who do not meet the eligibility screen criteria will be thanked for their interest, given a link to the Preeclampsia Foundation (http://www.preeclampsia.org/index.php) as an educational resource, and asked if they would be contacted for future research at the Brigham and Women's Hospital or at the Preeclampsia Foundation. If they select that they are interested in further research opportunities at the Brigham and Women's Hospital, they will have their names and contact information maintained on a contact list for future studies. Women interested in the Preeclampsia Foundation would be given a link to the Preeclampsia Foundation Registry (http://www.preeclampsiaregistry.com/). If they are interested in both, they will be added to the BWH list and given the link to the registry.

Step #2: Preliminary eligibility screen by short interview
Subjects meeting first eligibility on the REDCap screen will be contacted by study staff to complete a second step phone interview (submitted) with the Research Assistant. The Research Assistant will explain the study in further detail.

For women who answered the REDCap screen (Step #1) while still pregnant, a first phone call will be done to establish contact and confirm that the woman has been given a diagnosis of preeclampsia during the index pregnancy, confirm contact information, and obtain agreement from the subject to be re-contacted. A second phone call will be timed to fall at least 6 weeks after the expected delivery date. Women who are postpartum when they respond to Step# 1 will be called immediately. This phone screen will allow us to re-confirm with women that their pregnancy was complicated by preeclampsia, and that they meet other inclusion criteria. The phone screen will follow the guidelines as detailed in section IIIA of the PHRC website for pre-screening of research subjects during recruitment.

Subjects who are ineligible for study, and if interested, will be provided a link to the Preeclampsia Foundation as an educational resource (http://www.preeclampsia.org/index.php) to learn more about preeclampsia. They will also be asked if it is okay to keep their information on file for future studies at the Brigham and Women's Hospital. If subjects agrees to this, names and contact information will be maintained on a contact list for future studies at BWH

Subjects who are ineligible will also be asked if they want to learn about research being carried out by the Preeclampsia Foundation. Data for ineligible subjects will be filed without identifiers, to enable description of the source population.

Eligible subjects will proceed to Step #3.

Step #3: Obtain medical record release for review of pregnancy records to confirm qualifying preeclampsia diagnosis
If the subject appears to be eligible and wants to participate, a letter containing a medical record release form will be sent to her to obtain consent for the study team to obtain and review her pregnancy medical records to get details regarding the diagnosis of preeclampsia. Letters will contain a self-addressed stamped envelope for return of the form. Subjects will return the signed form back to us in that envelope.

Step #4: Review of Medical records
Once the signed medical record release form is received, study staff will contact physicians' and hospital offices to obtain copies of the medical records. Study staff will perform a standardized medical record review to confirm the preeclampsia diagnosis during the most recent pregnancy. The diagnosis of preeclampsia will be validated by a principal investigator. Medical records will be kept for the duration of the study, and stored securely in a locked cabinet in a locked office, accessible only to study staff as approved by the Principal Investigators and the IRB.

Step #5 Blood Pressure and Weight Eligibility Screening
Once a potential participant is confirmed as having had preeclampsia, she will be invited to the next phase of screening, verification that she is within the weight and blood pressure eligibility range. The study team will send a blood pressure monitor and scale (iHealth Wireless Blood Pressure Monitor, model BP5 and iHealth Wireless Scale Lite, model HS4) to the participant. Once she has confirmed receipt of these materials, the Research Assistant will contact the subject by phone to answer questions, and make sure that the subject knows how to use the devices. During that phone conversation, a study ID and a password as well as the address of the website for the study will be given to the subject.
This study ID will be used to enter and organize data. The link between the subject's name and the study ID will be kept in a secure file cabinet in a secure office area in the Division of Endocrinology, Diabetes, and Hypertension at the Brigham and Women's Hospital.

Subjects will install on their phones or tablets the free iHealth application to use the scale and blood pressure cuff. Subjects will use study ID and password provided. The account with the iHealth ID and password will be created by the study team.

The blood pressure monitor and scale will then be paired with the subject's Internet enabled device using Bluetooth technology via the iHealth application. The subject will then be asked to measure her blood pressure and her weight. The research assistant will be also available by phone to walk the subject through these steps as needed.

We will ask the subject to do these measurements, when possible, first thing in the morning. Subjects will be made aware that the completion of the weight and blood pressure measurements will take approximately 17 minutes. The subject will sit and rest for 5 minutes, then measure her blood pressure four times, each time 2 minutes apart. Measures will be sent electronically and automatically to a secure website. Then the

subject will weigh herself (by stepping on the scale with the application open), two times, each time a few minutes apart, and measures will be sent also electronically to our secure web-site (detailed below in section VIII). Instructions for the above steps will be sent with the kit.

Any subject with an average systolic blood pressure ≥ 140mm Hg (determined from the average over the four transferred measures) or with an average diastolic blood pressure ≥ 90mmHg and/or a BMI< 18.5 kg/m^2 or ≥40 kg/m^2 and/or a weight >350 lbs (determined from the average of the two transferred weights) will be excluded at this point. The research assistant will explain to them that that their blood pressure is higher than the study cut off, and be advised to follow up with a health care provider for redetermination of blood pressure, given the potential diagnosis of hypertension. Subjects with BMI < 18.5 kg/m^2 or ≥ 40 kg/m^2 and/or a weight >350 lbs will be informed that their weight or BMI exclude them from participation in the study as they do not meet the study cut offs. Excluded subjects will be mailed the Preeclampsia Foundation brochure entitled "Preeclampsia and Heart Disease" (brochure included as document) as well as a link to the Preeclampsia Foundation (http://www.preeclampsia.org), as an educational resource. If excluded subjects are interested in further research opportunities at the Brigham and Women's Hospital, we ask if we can keep their names and contact information on a contact list for future studies. If excluded subjects are interested in further research opportunities with the Preeclampsia Foundation, a link to the Preeclampsia Foundation Registry (http://www.preeclampsiaregistry.com/) will be sent. We will ask the excluded subjects to return the BP cuff and the scale in a pre-paid box, which we will send to the subject. This step will be done within the enrollment window from 3 up to 7 months and 0 days postpartum

The kit will also include the consent form in a sealed envelope for participation in the full intervention. This consent form will be sent with the kit to shorten the time it takes to enroll participants (detailed in Step #6). The envelope will be sealed so the subject will not read it before being totally eligible for the study after completing step #5.

Step #6: Procedure for obtaining the study consent form
After determining eligibility based on the blood pressure and weight criteria transmitted by the subject, the research assistant will contact the subject by phone, ask her to open the sealed envelope sent with the devices and will review in details the study consent form. All questions will be answered. Subjects will be given as much time as they want to read, review, and complete the consent form. Subjects who wish to discuss their participation in the study with others (family members, friends, physician) will be encouraged to do so. If the subject agrees, she will sign the consent form and will send it back to us.

We will stress that participation in our research study is voluntary, that subjects may withdraw from the study at any time, and that the investigators reserve the right to discontinue the research protocol at any time. Once, received, a study staff member will sign the consent form and a copy of the signed consent form will be sent to the subject and the version with the original signatures will be kept on file in the secure file cabinet.

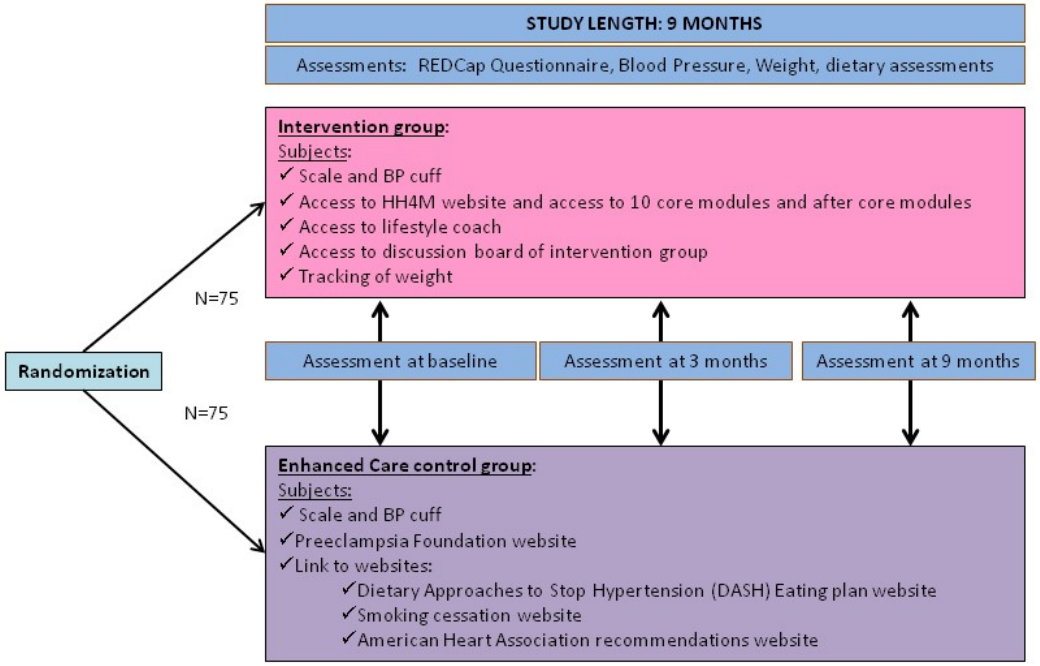
This step will be done within the enrollment window from 3 months postpartum up to 5 years and 1 month postpartum.

II. STUDY RANDOMIZATION

After the participant signed study consent form is received back by study staff, a computer program will generate random treatment assignments using a permuted block scheme with randomly varying block sizes to either the Lifestyle group or the Control Group.

III. STUDY

Women will start the study between 3 months postpartum and 5 years and 1 month postpartum. Both groups will follow the protocol outlined in the figure below.



Heart Health 4 Moms Schema

Both groups will receive:

Study participants in both arms will undergo 3 assessments: baseline (at the start of the study) and then after 3 months and 9 months in the study. All study participants will use the smart blood pressure monitor and a smart scale (received during the screening process) to transmit their blood pressure and weight data to the study's secure website. All study participants will complete REDCap questionnaires at the assessment points (as described below in section VII).

Subjects will be notified of their group randomization from the Research Coordinator through email, after the first assessment. Once randomized, the access to the website for all consented and randomized subjects will be modified: the subjects randomized in the Lifestyle groups will have access to all the features of this website (as described below). The subjects randomized in the Control group will have access to a website with limited information (as described below).

Control Group will receive:

Subjects in the Control Group will have access to only the following on the website:

- Basic information about the study
- Contact information of the research coordinator;
- Links to different websites:
    1) Preeclampsia Foundation website regarding cardiovascular risk after preeclampsia (http://www.preeclampsia.org/health-information/heart-disease-stroke)
    2) American Heart Association's diet and lifestyle recommendations website (http://goo.gl/YWwZGV);
    3) NIH Dietary Approaches to Stop Hypertension (DASH) website (http://www.nhlbi.nih.gov/health/health-topics/topics/dash);
    4) National Cancer Institute smoking cessation website (http://smokefree.gov/)

Lifestyle Group will receive:

During the 9 month intervention period, subjects in the Lifestyle Group (the active arm) will be provided access to internet-based lifestyle program with personalized coaching from a Lifestyle Coach by connecting with their username and password to our website. The coach is a registered dietician, trained in patient centered counseling and weight management. The lifestyle intervention is based on the original DASH (Dietary Approaches to Stop Hypertension) program, which was shown to lower blood pressure (Appel, 1997). Per the DASH diet, we will emphasize increased fruit and vegetable intake, whole grains, lean proteins and salt intake less than 2300mg/day. For women trying to lose weight (which we anticipate will be the majority), we will recommend a calorie deficit of 500kcal/day, and the Lifestyle Coach will work with participants to determine what that might consist of. Women who are breastfeeding and wish to lose weight will be counseled with a weight-maintenance diet, and the breastfeeding will provide the calorie deficit. Physical activity in the post partum period will be also addressed with the goals of building up to 150 min of physical activity weekly, based on strength training and cardio/aerobics.

The program will include educational modules with visual and audio. We will recommend that subjects watch/listen to one module each week for 12 weeks. Since the intervention is based on the use of educational modules in English and/or in Spanish, study subjects need to be able to understand English or Spanish at an 8th grade level. 8th grade literacy is determined using the Flesh Kincaid scale in English and the Fernández Huerta scale in Spanish. The modules include:

MODULE 1: Introduction to the program, the Lifestyle Coach and the team.

What is the link between preeclampsia and future health? How can we decrease our risk for future heart and blood pressure problems?

MODULE 2: What is the DASH eating plan? And how do we follow DASH?

MODULE 3: Balancing our plate

MODULE 4: How do we lower our salt intake?

MODULE 5: How to have family support?

MODULE 6: How do we attain/maintain a healthy weight and stay at it?

MODULE 7: How do we increase/maintain a good level of physical activity?

MODULE 8: Carbohydrates, Protein and Fat

MODULE 9: How do we read a nutrition label to make healthy choices?

MODULE 10: How do we stay on track and get back on track if we slip?

MODULE 11: How can we work with our health providers to optimize our future health?

MODULE 12: What's next?

During the 9 months of intervention, the Lifestyle Coach will use patient centered counseling strategies to help participants set positive lifestyle goals and motivate them to progress toward their goals.

A phone conversation with the Lifestyle Coach will be scheduled for week 1, week 3, week 6 (after half of the modules have been viewed), week 12 (at the end of the modules), month 6 and month 9 (completion of the study). The lifestyle coach will send an email to subjects at weeks 20, 28, and 32 weeks. Personal goals will be set up during the first phone call (eg weight loss goal and any other lifestyle change goals) and the next conversations will be used to reinforce these personal goals.

In addition to the modules and Lifestyle Coaching, participants in this arm will have the opportunity to obtain extra support for their lifestyle goals through interacting with the other subjects assigned to the lifestyle group as part of a member's only online community forum where they will be able to both give and receive support to other participants. Participants will be instructed to use only their first name or a pseudonym when interacting on the community forum. Participants may post questions to the group and communicate online in a protected environment. Only registered users (all participants randomized to the lifestyle group as well as the Lifestyle Coach) will be allowed to view and post to the blog. All forum entries will be reviewed by the Lifestyle

Coach to assure appropriateness. In the situation of the post being incorrect, the moderator will either correct it or delete it.

Subjects in the Lifestyle Group will informed that at the end of the study, they will have the opportunity to maintain access to the lifestyle website for a year.

Before beginning the intervention, the website will be piloted by women who have a history of preeclampsia and are currently serving in the Patient Advisory Council at the Preeclampsia Foundation. Any suggested changes that the study team decides to make based on the pilot will be submitted to the IRB for approval.

IV. STUDY ASSESSMENTS

a. Assessments (questionnaire) and parameters (blood pressure, weight and pregnancy status) to be measured: baseline, 3 months and 9 months

All women will be assessed at baseline, 3 and 9 months of study participation. A chart below depicts which domains will be assessed at which time points.
An email with a link to the questionnaires created on REDCap will be sent to the subjects in both arms.

Domains Assessed by Questionnaire (cf table below):

- Self-Efficacy toward healthy eating, physical activity and creation of a healthy home
- Social support toward healthy eating and physical activity
- Improvement in their behavioral risk (physical activity level, adherence to a healthy eating)
- Cardiovascular knowledge and risk perception
- Sleep quality, postpartum depression and breastfeeding status.

Parameters to be measured

Measure or domain	Baseline (3 m to 5 years 1 m pp)	3m in the study	9 m in the study
Demographics: race, age, parity, preeclampsia history, marital status, height	X		
Smoking, work schedule, recurrence of pregnancy	X	X	X
Primary Outcomes			
Self-Efficacy eating (Sallis modified)	X	X	X
Self-Efficacy exercise (Sallis modified)	X	X	X
Self-Efficacy household health (created for study)	X	X	X
Social support eating (Sallis modified)	X	X	X
Social support exercise (Sallis modified)	X	X	X
CVD Risk perception (Kim modified)	X	X	X
American Heart Association National Survey (modified)		X	X
Secondary Outcomes			
Blood pressure	X	X	X

Weight	X	X	X
Pregnancy Physical Activity Questionnaire (PPAQ) (modified for postpartum women)	X	X	X
Other Measures			
Food Frequency Questionnaire adapted from the DASH online questionnaire and the Arizona Food Frequency questionnaire	X	X	X
Pittsburgh Sleep Quality Index	X	X	X
Project Viva breastfeeding	X	X	X
Edinburgh Postpartum Depression Scale (EPDS)	X	X	X
Health Care Use	X	X	X
Self-efficacy toward smoking cessation	X	X	X

Questionnaires forming the source of items for our questionnaires

1. Demographic Questionnaire (Derived from items on the Behavioral Risk Factor Surveillance System (BRFSS). http://www.cdc.gov/brfss/questionnaires/pdf-ques/2013%20BRFSS_English.pdf
2. Sallis Self Efficacy Survey for Diet and Exercise Behaviors http://www-rohan.sdsu.edu/faculty/sallis/self-efficacy-coverandexercise.pdf
3. Sallis Social Support for Healthy Eating and Physical Activity http://sallis.ucsd.edu/measure_socialsupport.html http://sallis.ucsd.edu/measure_socialsupport.html
4. Cardiovascular Risk Perception Score, based on the Kim questionnaire for Gestational Diabetes http://care.diabetesjournals.org.ezp-prod1.hul.harvard.edu/content/30/9/2281.full.pdf+html
5. Pregnancy Physical Activity Questionnaire (PPAQ) http://www.luzimarteixeira.com.br/wp-content/uploads/2010/08/development-validation-pregnancy.pdf
6. Project Viva Breastfeeding questionnaire from Celi et al (Celi, 2005)
7. Pittsburgh Sleep Quality Index http://www.sleep.pitt.edu/includes/showFile.asp?fltype=doc&flID=2532
8. Edinburgh Post-Partum Depression Scale (EPDS). http://www.fresno.ucsf.edu/pediatrics/downloads/edinburghscale.pdf
9. DASH Online Questionnaire from Apovian et al (Apovian, 2009)
10. Arizona Food Frequency Questionnaire http://azcc.arizona.edu/sites/azcc.arizona.edu/files/AFFQteal.pdf
11. Self-efficacy on smoking cessation from Etter and al. (Etter, 2000)

For this study, all adapted questionnaires except for the food frequency questionnaire will be combined into one single study questionnaire to make the questionnaires user-friendly. The single questionnaire will be created on REDCap and a link for it will be emailed to the subjects at time of the assessments, as well as a reminder for taking their measurements. Subjects will have a two week window around their 3 study dates to

complete each assessment. Should the subject miss their two week window to complete their assessment, a follow-up phone call will be made.

The food frequency questionnaire will be administered as a stand-alone measure at baseline, 3 months, and 9 months.

Measurement of Weight and Blood Pressure

Subjects will be informed that the completion of the weight and blood pressure measurements will take approximately 17 minutes and should be taken if possible first thing in the morning. The subject will sit and rest for 5 minutes, then measure her blood pressure four times, each time 2 minutes apart. Measures will be sent electronically and automatically to our secure website. Then the subject will weigh herself (by stepping on the scale with the application open), two times, each time a few minutes apart, and measures will be sent also electronically to our secure website. We will instruct the subject to not share their devices with their family members during the outcomes measurements dates. We will ask the subjects to specify the dates they are doing their measurements to allow us to retrieve the measurements (as explain below).

Monitoring for Safety and Possible Exclusion

At consent, subjects will be informed that the study questionnaires and their measures of blood pressures and weight will not be reviewed until completion of the entire study.

- Blood pressures: Blood pressures will be requested manually by study staff using a query tool that uses an active call through the iHealth API for each assessment date, which will be specified by each subject. Subjects will be educated that if their blood pressure were to be higher than 140 mmHg for the systolic and/or higher than 90 mmHg for the diastolic they should contact their health care provider within the next two weeks. If a subject reports a diagnosis of hypertension, she will be encouraged to continue in the study unless her health care provider says otherwise. Following the recommendations of blood pressure monitoring at home from the American Heart Association, if at any time, a systolic blood pressure is measured at or higher than 180 mm Hg and/or a diastolic blood pressure is measured at or higher than 110 mm Hg, the subject will be instructed to re check her blood pressure again immediately and if the blood pressures are elevated again to the same parameters to seek immediate emergency care (http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/SymptomsDiagnosisMonitoringofHighBloodPressure/Symptoms-Diagnosis-Monitoring-of-High-Blood-Pressure_UCM_002053_Article.jsp).These instructions will be explained in the consent form, and displayed on the website as well, accessible 24/7 to all subjects. If at any point the subject will experience symptoms such as headaches, shortness of breath or chest pain associated with blood pressure at or higher than 180 mmHg for the systolic and/or at or higher than 110 mm Hg for the diastolic, the subject will be instructed to seek immediate emergency care

- Weight: Women weighing more than 400 lbs should not use the scales, which are safety-rated only to 400 lbs. A woman reaching 380 lbs will be educated to check her weight again within the next 7 days and if a weight >380lbs is confirmed, she will be educated on not to weigh herself any more during the study, but she will be able to continue the study, as explained in the consent form and as displayed on the website accessible 24/7.
- Pregnancy status: This intervention is not designed for pregnant women given the coaching around weight management, which would not be the same for pregnant women as for non-pregnant women. Women who become pregnant during the study will be excluded from the study. We will ask about pregnancy status at baseline, 3 months, and 9 months. We will also ask women to alert us if they become pregnant.

b. Qualitative interviews

After completion of the 9 month study assessment, all subjects will be invited via email to participate in an informant interview to detail their experience using the program, what they liked and disliked about the program, and how the program could be improved. A research assistant will contact each interested subject by phone to conduct the interview. Subjects will be reminded that participation in the interview is voluntary, be informed about how we will protect their privacy, and be told that they can skip any question. Subjects will verbally consent to participating in the interview and to having the phone call recorded and transcribed.

c. Drugs to be used: none

d. Devices to be used: Subjects will use a scale and a blood pressure monitor from iHealth.

- Scale: iHealth Lite Scale model HS4 from iHealth
- BP monitor: Wireless Blood Pressure Monitor model BP5 from iHealth

e. Procedures/surgical interventions: none

V. BIOSTATISTICAL ANALYSIS

a. Specific data variables being collected for the study include:

Specific data variables being collected for the study include (cf table below):

1) Data collected from the REDCap screen
2) Data collected on the screen
3) Data collected from the medical records review
4) Data collected by the scale and the BP monitor
5) Data collected from the questionnaires

6) Data collected from phone conversation between the subjects and the Research Assistant and/or the Lifestyle Coach.

Study endpoints:

1) Primary endpoints:
   - Increased self-efficacy for eating and physical activity, as assessed by the Sallis self-efficacy questionnaires (change from baseline to 3 and 9 months).
   - Increased self-efficacy toward the construction of a healthier home, as assessed by our questionnaire (change from baseline to 3 and 9 months).

- Increased knowledge of cardiovascular risk, as assessed by the Kim questionnaire (change from baseline to 9 months) and by the AHA questionnaires (differences between the two groups at 3 and 9 months).
- Improved behavioral risk factors:
- Increased compliance with the DASH Eating Plan pattern
- Increased level of physical activity

2) Secondary endpoints:
   - Weight (change from baseline to 3 and 9 months)
   - Achievement of weight goals (at 3 and 9 months)
   - Achievement of pre-pregnancy weight (at 3 and 9 months)
   - Systolic blood pressure and diastolic blood pressure (change from baseline to 3 and 9 months)
   - Development of hypertension (at 3 and 9 months)

b. Statistical methods

Analytic Methods: Analyses will begin by examining the extent to which baseline patient characteristics (including age, blood pressure, BMI, preeclampsia severity) are distributed evenly between arms. The main analyses will quantify the effectiveness of the intervention through 'intention-to-treat' (ITT) analyses including every randomized participant, regardless of program completion or compliance. Based on the experience of our post-GDM program (Nicklas, 2014), we expect only a small degree of patient drop-out and missingness of endpoint data (see below for a detailed discussion of the proposed methods for handling missing data). The primary outcomes will be analyzed using a general mixed-effect model for repeated measures (MMRM), a special form of the general mixed-effects regression model for longitudinal data. The MMRM analyses will be implemented via PROC MIXED in SAS. Specifically, post-baseline values of the primary outcomes (or, equivalently, changes from baseline) are assessed as the response variables in a longitudinal regression analysis; the covariates in the regression model include the categorical effects of treatment (or Intervention), time (months 3 and 9 since baseline), and treatment-by-time interaction, along with the continuous effects of baseline response and baseline-by-time interaction. This adjustment for baseline response as a covariate in the regression model is analogous to a type of multivariate ANCOVA. We also note that this method of adjustment is more statistically powerful than examining either unadjusted endpoint values or pre- to post-intervention change in endpoints. Treatment-by-time interaction contrasts will be constructed that provide direct estimates and statistical tests of the difference between intervention groups in mean change from baseline to 3 and 9 month endpoints. Finally, an unstructured covariance matrix will be used to model the within-subject errors or correlation among the repeated measures on the same subject. The advantage of using an unstructured covariance is that no assumptions are made about the within-subject variability.

Heterogeneity of Treatment Effect by Patient Characteristics: We will examine heterogeneity of treatment effect by patient baseline characteristics. These subset analyses will use multivariable modeling (linear and logistic regression models) to test for multiplicative interaction (using cross-product terms) and additive interaction

(using the Relative Excess Risk of Interaction (RERI) index) between treatment assignment and factors that might modify the success of the program; a p-value less than 0.05 will be indicative of heterogeneity. We will examine the following pre-specified factors:

□ Baseline overweight: we will stratify analysis by baseline BMI<25 vs. ≥25 kg/m^2. If more statistical power is necessary, we can examine the interaction of continuous baseline BMI with the intervention.

□ Baseline prehypertension: we will compare the effectiveness of the program among women who are normotensive and prehypertensive. As with BMI, we can test a term representing interaction of continuous BP with intervention.

□ Severity of preeclampsia: we will examine whether the program is more or less effective among women with more or less severe preeclampsia

□ Patient education level, baseline knowledge of CVD risk, baseline self efficacy, race/ethnicity, English- or Spanish-language program use, recruitment source (NACCHO referral, Craigslist, Preeclampsia Foundation, other).

Analyses of Adherence and of Mediators: Although we expect good adherence to the protocol, if overall adherence is <80%, as measured by number of modules accessed, we will conduct secondary analyses adjusted for individual compliance. In exploratory analyses, we will also identify mediators of the intervention effect by introducing the mediator into the model and assessing the proportion of treatment effect (PTE) attributable to the mediator (PTE=1 – β/α, where β is the coefficient for treatment in the model without the mediator and α is the treatment coefficient when the mediator is included) and its 95% confidence interval. We will not assume interactions between the treatment and the mediator. For example, adjusting for physical activity may illuminate how much weight loss is attributable to activity versus other pathways. These secondary analyses will be interpreted with caution, as they no longer constitute randomized analyses.

Avoidance of bias: a randomized controlled trial is the 'gold standard' of study design, because it minimizes selection and confounding bias. So that we will not admit selection bias by differential patient adherence, we will follow the 'intention-to-treat' (ITT) principle throughout analysis.

Missing data is a key issue in the analysis of data from this study. While extensive efforts will be made to minimize missing data, a relatively small number of subjects are anticipated to drop out. Incomplete data poses two concerns: efficiency and bias. For all planned analyses, we will use statistical methods that incorporate partially observed data on subjects who drop out (e.g., linear mixed effects models). Based on a "missing at random" (MAR) assumption, the likelihood-based MMRMs provide valid inferences on intervention effects when there is incomplete data; no explicit imputation of the missing data is required. We will also provide detailed descriptions of the patterns of missing data and assess the sensitivity of results to different assumptions about the mechanism by which data is missing using multiple imputation methods. Specifically, in the spirit of sensitivity analyses, we will consider multiple imputation of missing data using either a parametric regression method that assumes multivariate normality or a nonparametric method that uses propensity scores. Each of these two imputation models, along with the procedure for combining multiple sets of

point and variance estimates for the intervention effects, can be implemented using PROC MI and PROC MIANALYZE in SAS (SAS Institute, Inc., 2004). This type of sensitivity analysis of incomplete data is consistent with the guidelines set forth in the National Research Council (NRC) document on incomplete data in clinical trials (Little, 2010).

The primary risk to validity in this study is the possibility that patients in the control group will be alerted to their CVD risk and may seek to lose weight and reduce blood pressure; to the extent that they are successful, this would bias results toward the null. However, there is also the likelihood that participants in the intervention group will be somewhat more motivated by being in a study than they might be if they were using the program in the 'real world', which would bias away from the null. These biases should be modest at most, and are likely to cancel each other out.

VI. RISKS AND DISCOMFORTS

Due to the non-invasive nature of the proposed study, potential risks of participation are minimal. The investigators have extensive experience in the study intervention and assessments.

a. Complications of surgical and non-surgical procedures

1) Questionnaires: It may be tiring to fill out the questionnaire, but the subject will have the possibility to do it with pauses. Also, a participant may feel uncomfortable answering questions of a personal nature, but subjects can always choose not to answer any question.
2) Determination of Blood Pressure: The blood pressure cuff may cause a sensation of pressure when it is inflated. This sensation will resolve with cuff deflation. Subjects whose blood pressure is in the hypertensive range (either at study screening or during the course of the study) will be advised to see a medical provider to confirm the elevation. Therefore, participation in this study may lead to the diagnosis of hypertension. We believe this to be a benefit allowing the woman to receive earlier treatment.
3) Confidentiality: The Principal Investigator and her staff will take all reasonable measures to protect the confidentiality of each subject's records and data. Subject data will be referenced by subject number only. Research data will be kept in a secured file cabinet in a secured office area in the Division of Endocrinology, Diabetes, and Hypertension as well as in a secure folder computer database. Research data kept online will be kept secure and confidential through extensive password protection, username anonymity.

b. Drug side effects and toxicities: none

c. Device complications/malfunctions:

1) Blood pressure cuff and scale: Women may have technical difficulties regarding the use of the BP cuff, or scale. They will be provided with manufacturer information on how to use the devices. In addition, the Research

assistant is very familiar with their functioning and will be available to address potential technical issues. If the scale or BP cuff are deemed non functional after the research coordinator has worked with the subject, a new device will be mailed to the subject with a pre paid box in which to return to study staff the defective device. The scale may break if 400 or more lbs are placed on it, as the scale is safety-rated only to 400 lbs. A woman reaching 380 lbs will be asked to check her weight again within the next 7 days and if a weight >380lbs is confirmed, we will ask her to not weigh herself any more during the study, but to continue the study.

d. Psychosocial (non-medical) risks: none anticipated

e. Radiation risks: none

VII. POTENTIAL BENEFITS

a. Potential benefits to participating individuals

There may be no individual benefit from participation in the study. This study will explore the hypothesis that a novel lifestyle intervention program modeled upon the DASH program for postpartum woman with a recent history of preeclampsia can successfully affect healthy diet and physical activity habits leading to increased self-efficacy for healthy eating and physical activity, increased knowledge of their cardiovascular risk and possibly leading to weight loss and a reduction of blood pressure. We believe that the importance of gaining this knowledge outweighs the minimal risk posed to the subjects. Some women in both groups may have the early diagnosis of hypertension during the study and therefore be able to receive earlier care for this condition. Women in both arms will have access to the online modules (during the study and an additional year for the lifestyle group and after completion of the study for the control group).

b. Potential benefits to society

Lifestyle intervention programs like the DASH program remain an extremely effective treatment for reducing high blood pressure; however, they have not been tested in a population of women with recent preeclampsia. Identifying lifestyle programs that are effective in this population may be therapeutically useful in this segment of the population with an elevated risk for developing cardiovascular diseases.

VIII. MONITORING AND QUALITY ASSURANCE

Key personnel are:

1. Ellen W. Seely, MD – Principal Investigator
2. Janet Rich-Edwards, ScD- Principal Investigator
3. Louise Wilkins-Haug, MD- Co-Investigator
4. Geraldine Skurnik, MD – Research Fellow
5. Andrea Roche, RD – Lifestyle Coach
6. Jennifer Stuart, MSc – Data Analyst
7. Joeli Katz, MA – Research Coordinator
8. Garrett Fitzmaurice, ScD – Statistician
9. Grace Chen, BA – Research Coordinator

Data Management: The Principal Investigators, Drs. Ellen Seely and Janet Rich-Edwards, will prepare and maintain complete and accurate study documentation in compliance with good clinical practice standards and applicable federal, state, and local laws, rules, and regulations. Study documentation shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by any regulatory agency. The investigator will promptly take any reasonable steps that are requested as a result of an audit to correct deficiencies in the study documentation. Data confidentiality will be maintained and regulations regarding access to data by those other than the study staff will be followed. All information will be entered into the study dataset by coded entry only. The code identification data will be kept in a locked file available only to the principal investigator unless requested by the appropriate regulatory authority as well as in a secure folder computer database.

REDCap: REDCap is a secure web-based application, licensed by Partners.

Website: The study will have a password-protected website accessible only to study participants who have been given a system-generated user name and password to log in. Any registration or login information requiring transmission will be sent using 256 Bit SSL Certificate Encryption. The site will be cloud-hosted on a secure server. Personal information residing on the server will be de-identified and identifiable only by user name.

Progress Reports: Annual progress reports will be submitted to the IRB and the PCORI describing all of the study activities.

a. Independent monitoring of source data: none

b. Safety monitoring:
There will be two independent data safety monitors who are not directly involved with the study.

Gail Adler, MD, PhD, Associate Professor of Medicine, Harvard Medical School is an endocrinologist and accomplished clinical researcher in the area of diabetes.
Chloe Zera, MD, MPH, Assistant Professor of Obstetrics and Gynecology, Harvard Medical School and is an obstetrician with a specialty in Maternal Fetal Medicine and a clinical researcher at BWH.
They will be notified of any serious adverse events simultaneous with notification of the Brigham and Women's Hospital Institutional Review Board. Every six months, they will review study records to monitor protocol adherence to inclusion and exclusion criteria and to study staff adherence to the protocol concerning self-report of pregnancy (exclusion from continuing study), referral of women with elevated blood pressures to a health care provider and instruction of women with high BMI to no longer use the scale.

c. **Outcomes monitoring:** The Research Fellow will inform the Principal Investigators, Dr. Ellen Seely and Dr. Janet Rich-Edwards, of any participants whose blood pressures are in the hypertensive range, whose weights reach 380 lbs, or who become pregnant. For any participant whose blood pressures are confirmed elevated, one the Principal Investigator will contact the participant to convey this information and make recommendation for her to be seen by a health care provider. For any participant whose weight is confirmed to be at 380 lbs or higher, the Research Assistant will contact her within 2 business days to make sure she will not be using anymore the scale. These subjects will stay in the study. If a subject becomes pregnant, one of the Principal Investigators will contact the participant let her know she cannot participate in the study anymore. The study staff will be responsible for notifying the Principal Investigators regarding any participant complaints or any other safety concerns that may arise during the study; the Principal Investigators will document these instances and will respond appropriately. All safety issues and participant complaints will be reviewed with the Data Safety Monitors every six months, or more often in the case of issues that are not easily resolved.
d. **Adverse event reporting guidelines:** The Principal Investigators are responsible for reporting all adverse events according to the Human Research Committee's guidelines. Expected and unexpected adverse events associated with this protocol will be reported to the Institutional Review Board (IRB) within 72 hours. Any serious adverse events will be reported to the above committees and to the appropriate office at PCORI and other sponsor within 24 hours.

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