Reducing Cardiovascular Risk in Perimenopaual Latinas: Pilot Study of a Multi-Component Intervention

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Principal Investigator: Yamnia Cortes
Sponsor: **University of North Carolina at Chapel Hill**
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Revisions to Version Number: v.1.000 (28 March 2020)
Version Number: v.2.000 (20 June 2020)
Version Number: v.3.000 (09 August 2021)

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
5.5., 6.0, 8.0	Procedures may be conducted virtually. In-person visits for data collection should be performed with proper facial covering and sanitizing. Prior to scheduling visits, research assistants must ask about COVID-19 symptoms and exposures (see attachment). During screening, participants will receive information about participating in a research study during COVID-19.	Due to the COVID-19 pandemic we have adjusted procedures to reduce in-person contact and assess risk of COVID-19 exposure.
5.0	The inclusion criteria was updated to include women 40-60 years and women who are early postmenopausal (1-2 years since final menstrual period). The counties for randomization are Durham and Wake versus Orange, Chatham, and Alamance.	We expanded the inclusion criteria to increase our community outreach. Women that are early postmenopausal also experience hormone changes and arterial remodeling, which is related to increased CVD risk.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).
- National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

Principal Investigator or Clinical Site Investigator:

Signed: Yamnia Cortés Date: 3-1-2020

Name*: Dr. Yamnia I. Cortés
Title*: Principal Investigator

Investigator Contact Information:

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Reducing Cardiovascular Risk in Perimenopaual Latinas: Pilot Study of a Multi-Component Intervention

Grant Number: 1K23MD014767-01

Study Description:

Cardiovascular disease (CVD) is the leading cause of death among Latinas, exceeding rates for Latino men. Evidence suggests that Latinas have a significantly worse CVD risk factor profile than non-Hispanic White women. Furthermore, Latinas are considerably less likely to meet physical activity and dietary guidelines than non-Hispanic White women, particularly during perimenopause. Prior studies have shown that increases in CVD risk can be prevented in perimenopausal women using a lifestyle dietary and physical activity intervention; however, these studies did not include Latinas. To address these deficits, the aim of this study is to pilot test a multi-component behavioral intervention among perimenopausal Latinas (age 40-55) that integrates evidence-based education with physical activity, stress management, and coping skills training to: **1)** reduce biologic CVD risk, including adiposity, blood pressure and arterial stiffness; **2)** improve nutrition, physical activity, and sleep; and **3)** improve stress management, coping strategies, and self-efficacy.

Objectives*:

Primary Objective:	To examine the feasibility and initial efficacy of the multi-component behavioral intervention to reduce biologic CVD risk from Time 1 (baseline) to each of Time 2 (6 months) and Time 3 (12 months).
Secondary Objectives:	To evaluate the initial efficacy of the intervention to improve secondary outcomes of health behaviors, adiposity, inflammatory and stress biomarkers, and vasomotor symptoms from Time 1 (baseline) to each of Time 2 (6 months) and Time 3 (12 months).

Endpoints*:

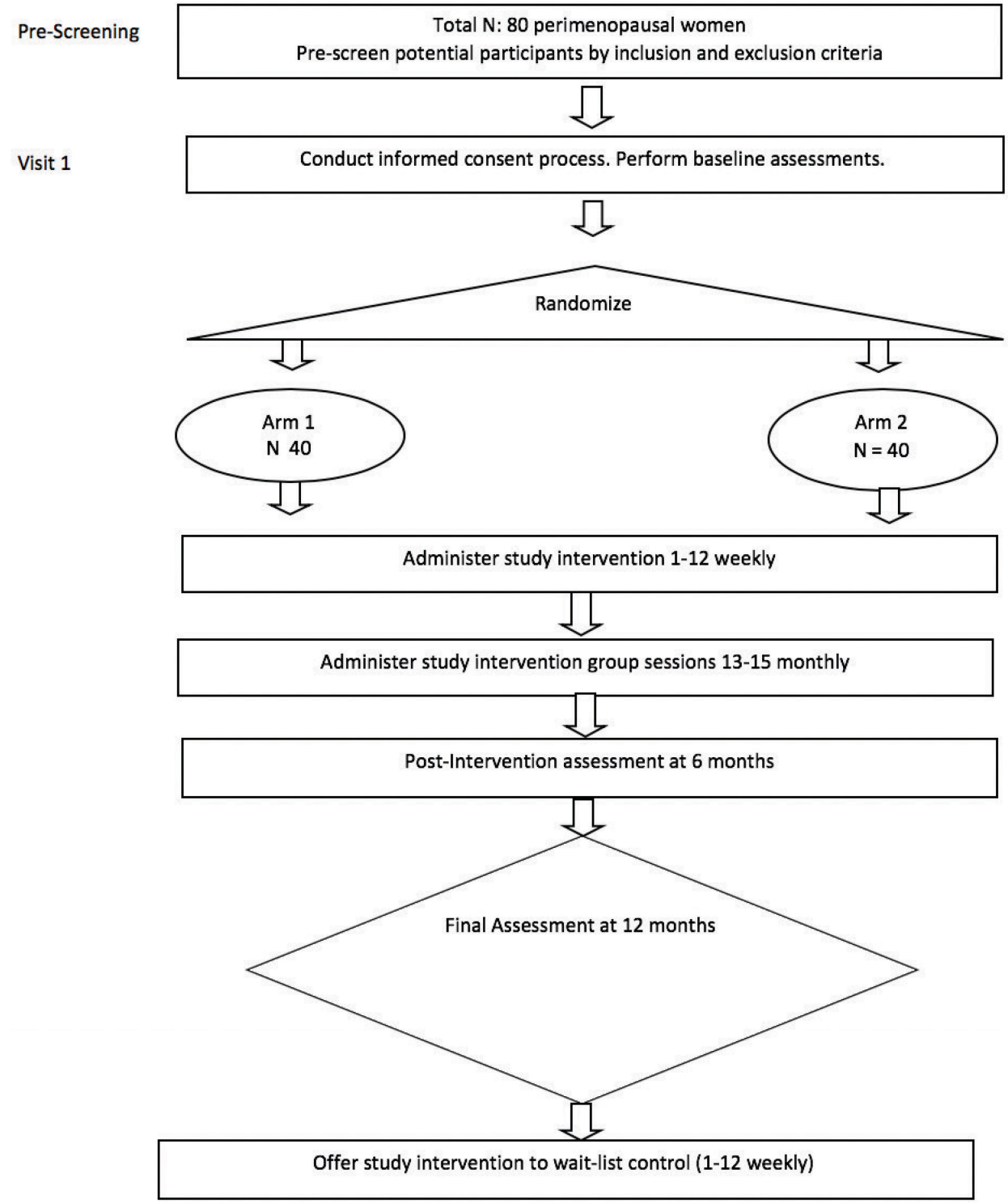
Primary Endpoint:	**a)** Feasibility: enrollment and retention rates; barriers and facilitators to enrollment; intervention fidelity; suitability of study procedures and outcome measures; and participant satisfaction with the intervention and study protocol. **b)** Biologic CVD risk: blood pressure, arterial stiffness, lipids, blood glucose.
Secondary Endpoints:	**a)** Health behaviors: nutrition, physical activity, sleep, coping strategies.

b) Other biological factors: adiposity, inflammatory and stress biomarkers, vasomotor symptoms.

Study Population:	A total of 80 perimenopausal Latinas.
Phase* or Stage:	Cluster randomized controlled with an experimental and wait-list control group.
Description of Sites/Facilities Enrolling Participants:	Participants recruited from community sites in Durham, Wake, Orange, Alamance, and Lee Counties in North Carolina.
Description of Study Intervention/Experimental Manipulation:	An experimental group of women receive an intervention consisting of *Su Corzaón Su Vida* education sessions, group physical activity, stress management, and coping skills training. The wait-list control group is offered the intervention at the end of Time 3 (12 months).
Study Duration*:	A total of 4 years or 48 months.
Participant Duration:	Each participant will be in the study a total of 12 months.

1.2 SCHEMA

Flow Diagram



1.3 SCHEDULE OF ACTIVITIES

Summary of Variables, Measurement, and Data Collection Time Points			
Variables and Measurement	**0**	**6**	**12**
Feasibility			
*Process evaluation checklist (bi-monthly)	--	--	--
*Screening and enrollment logs	X	X	X
*Intervention attendance	X	X	X
*Data collection attendance	X	X	X
Exit interview			X
Biological CVD Risk Factors (Primary Outcomes)			
Systolic and diastolic blood pressure	X	X	X
Fasting blood glucose	X		X
Fasting lipid profile	X		X
Arterial stiffness (carotid-femoral PWV)	X		X
	X		X
Health Behavior (Secondary Outcomes)			
Nutrition and food security	X	X	X
Physical activity questionnaire	X	X	X
Accelerometer (7 days, 24 hours/day)	X	X	X
Sleep questionnaire	X	X	X
Perceived stress	X	X	X
Coping response inventory	X	X	X
Eating self-efficacy scale	X	X	X
Exercise self-efficacy scale	X	X	X
Biological Influences (Secondary Outcomes)			
Height, Weight, BMI	X	X	X
Waist Circumference	X	X	X
Hair Cortisol and Hs-CRP	X		X
Vasomotor symptoms questionnaire	X	X	X
Demographic, Sociocultural, and Environmental	X	X	X
Demographic questionnaire (e.g., age, education)			
Acculturation questionnaire (e.g., years in US)			
Everyday discrimination scale			
Brief resilience scale			
Health history questionnaire			
Reproductive history questionnaire			
Community food assessment			
Neighborhood risk assessment			
Physical activity resource assessment			

0 = baseline; 6 = 6-month (completion of intensive intervention and continued support); 12 = 12-month (after 6 months of maintenance on own); BMI = body mass index; Hs-CRP = high-sensitivity C-reactive protein; PVW = pulse wave velocity

*Completed by Project Manager

2 INTRODUCTION

2.1 STUDY RATIONALE

Background: CVD remains the leading cause of death for women globally. In women, risk of CVD increases substantially during perimenopause. Latinas have a significantly worse CVD risk factor profile than non-Hispanic White women, attributable to several factors including lower socioeconomic position, interpersonal violence, discrimination, and stress. These factors are related to CVD through their influence on health behaviors as well as potential mechanisms involving inflammatory and neuroendocrine pathways. Despite their increased risk, however, perimenopausal Latinas remain underrepresented in CVD research.

Methods: This study is guided by the National Institute of Minority Health and Health Disparities (NIMHD) Framework, which considers the interplay between sociocultural environment, built environment, behavioral influences, and biological influences on health. Using a cluster randomized two-group, repeated measures experimental design, the goal of this study is to investigate the feasibility and initial efficacy a 12-monthintervention integrating evidence-based education and coping skills training with physical activity and stress management. The intervention has three phases: 12 weekly sessions (Phase I: education, physical activity, stress management, coping skills training) followed by 3 monthly sessions of continued support (Phase II); and finally 6 months of skill maintenance on their own (Phase III). Measurement visits will occur at baseline, 6, and 12 months. We will conduct in-depth exit interviews with participants to assess barriers and facilitators to recruitment and enrollment, delivery of the intervention, fidelity, and suitability of assessment procedures. We will partner with local churches and community centers in two counties to recruit participants and deliver the intervention. Data will be collected at Time 1 (0 months [baseline]) to Time 2 (6 months [completion of the intervention]) and Time 1 to Time 3 (12 months [after 6 months with no contact from the study staff]). Data collected will include blood pressure, lipid profile, blood glucose, and arterial stiffness. Secondary outcomes will include health behaviors and self-efficacy, adiposity, inflammatory and stress biomarkers, and vasomotor symptoms.

Discussion: This study will contribute to knowledge on the feasibility of behavioral interventions including stress management and coping skills training delivered by CHWs, which could reduce CVD burden among perimenopausal Latinas.

2.2 BACKGROUND

CVD, including coronary heart disease and stroke, is the leading cause of death among Latinas (29%), exceeding rates for Latino men (27%) [1]. Despite being at greater risk for CVD, only 34% of Latinas are aware that CVD is the leading cause of death in women [2]. Although several national organizations have developed initiatives to raise understanding about CVD among Latinas, as yet Latinas remain considerably less likely to meet physical activity and dietary guidelines than non-Hispanic White women, particularly during perimenopause [3]. Perimenopause is marked by dramatic changes in sex hormone levels, which may adversely

affect CVD risk factors such as body fat, insulin secretion, and lipoprotein levels [4,5]. Perimenopausal Latinas have lower estrogen and higher follicle stimulating hormone levels than non-Hispanic White women [6],which can increase the risk for CVD. Thus, perimenopause is a critical window for CVD prevention among Latinas.

The sociocultural environment includes beliefs, customs, and values of a population. The sociocultural environment of perimenopausal Latinas may include poverty and limited English proficiency, both of which are associated with lower healthcare access [6,7].Studies among women age 40-65 years have shown that chronic stress, job strain, and discrimination may increase biologic CVD risk through their influence on health behaviors [8,9]. Latinas are particularly at risk for CVD during perimenopause because they may experience acculturative stress and social isolation, resulting in adverse health behaviors such as increased sedentariness [10,11]. This study addresses the sociocultural environment by providing peer education using community health workers (CHWs), support, and resources to improve Latinas' health in context of their everyday lives. Peer education using CHWs has been shown to improve diet, physical activity, and weight [12].

The built environment encompasses all buildings, spaces, and structures where individuals live, work, and play [13]. This study focuses on the neighborhood-level built environment, including accessibility to safe parks/recreation areas and supermarkets or produce grocers. Disadvantaged neighborhoods have a high concentration of poverty and unemployment, which influences crime rates, availability of public services, parks, grocery stores, and fast food and liquor establishments [14]. Many Latinas live in neighborhoods with only 32% as many grocery stores as less disadvantaged communities and thus lack access to healthy food [15]. Living in disadvantaged and unsafe neighborhoods increases stress [16], limits physical activity and increases sedentary behavior [17,18], which influence biologic CVD risk factors such as blood pressure, cholesterol, adiposity and inflammation [19,20]. To address the built environment, our intervention will provide women with information on where to access healthy low-cost food and safe spaces for physical activity.

The most consistent behavioral factors contributing to CVD risk during perimenopause are inadequate nutrition, decreased physical activity [21], poor sleep patterns [22], and chronic stress [23]. Social cognitive theory [24] posits that enhancing an individual's knowledge and skills to perform a new behavior improves self-efficacy, which in turn increases likelihood that the new behavior will be maintained. National reports have shown that <16% of adult Latinas consume the recommended servings of whole grains, fruits, and vegetables [25]. The Hispanic Community Health Study/Study of Latinos has reported that only 27% of Latinas age 45-64 years meet the national guidelines for physical activity [26]. In addition, over half of perimenopausal Latinas report difficulty sleeping [27], which has been associated with arterial stiffness [28], a hardening of the vessel wall often predictive of CVD [29]. Latinas report higher levels of perceived stress compared to perimenopausal women of any other race/ethnicity in the US [30]. In this study, we will facilitate behavioral change and improve self-efficacy in perimenopausal Latinas by helping them acquire coping strategies for problem-solving, communication, stress management, and cognitive behavioral modification.

Prior interventions have been successful in increasing knowledge of CVD risk, physical activity, and heart-healthy diet among Hispanics/ Latinos [31,32]. Many of these interventions have incorporated an evidence-based CHW-led curriculum—*Su Corazón, Su Vida (SCSV)—a* 12-lesson curriculum consisting of information on CVD risk awareness, healthy food choices, and physical activity [33]. The curriculum has been used among Latinos age 18 and older in the US and Mexico, with success in improving health behaviors [31,32]. Most interventions incorporating *SCSV*, however, have been education only, with either a short follow-up (<6 months) [31] or no assessment of biologic CVD risk [33]. Our study will address important limitations of prior interventions. We will pilot test a novel multi-component behavioral intervention integrating evidence-based education (SCSV) with coping skills training, physical activity sessions, and stress management. This is a new multi-component intervention to reduce biologic CVD risk (blood pressure, arterial stiffness, lipids, blood glucose) and to improve health behaviors (nutrition, physical activity, sleep, coping strategies, self-efficacy, stress management) among perimenopausal Latinas.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risks to Human Subjects
Institutional Review Board (IRB) approval was obtained from The University of North Carolina at Chapel Hill (UNC-CH). Using a cluster randomized two-group, repeated measures experimental design, the goal of the study is to investigate the feasibility and initial efficacy of a 12-month intervention consisting of: **Phase I)** 12-week nutrition and exercise education, physical activity group sessions, coping skills training, and stress management intervention in perimenopausal Latinas; **Phase II)** 6 months of continued monthly contact to help women improve health behaviors and self-efficacy; and **Phase III)** 6 months of health maintenance without contact from study staff. We will partner with community centers to enroll women and we will partner with two churches in two North Carolina counties to deliver the intervention.

Inclusion criteria include age 40-60 years; self-identify as Latina; understand spoken English or Spanish; perimenopausal (menstrual bleeding in the past three months, but timing of periods have varied in past year, or no menstrual bleeding in the past 3-11 months) or early postmenopausal (1-2 years since final menstrual period); intact uterus and at least one ovary; not currently pregnant; no hormone therapy or oral contraceptives in the past three months. Potential participants will fill out a health history questionnaire to ascertain if they have a history of CVD (heart attack, stroke, coronary heart disease), heart murmur, congenital heart disease, family history of sudden death, difficulty walking or exercising. Women who answers yes to any of these health history questions will be excluded from the study and referred to a health care provider. After enrollment and baseline assessment, two churches in two counties will be randomly assigned to either the intervention or control group. Participants will be assigned to the group in their respective county. Participants will be informed of their group assignment by telephone.

Data will be collected at Time 1 (baseline [0 months]), Time 2 (post Intensive Intervention and Continued Support [6 months]), and Time 3 (6 months after completion of Continued Support [12 months]). Data collected will include the primary outcomes of blood pressure, arterial stiffness based on carotid-femoral pulse wave velocity measures, lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides), blood glucose; secondary outcomes of health behaviors (Sleep Quality Questionnaire, Food Behavior Checklist, Physical Activity Questionnaire, and 7-day Accelerometer), self-efficacy (Eating Self-Efficacy Scale and Exercise Self-Efficacy Scale), body mass index, waist circumference, hs-CRP, hair cortisol, and vasomotor symptoms. We will also evaluate the feasibility of the study including, number of eligible participants; methods of identifying/recruiting participants; willingness of participants to be randomized; practicality of delivering the intervention in the proposed setting; enrollment and retention rates, and suitability of the intervention and assessment protocol. Data analysis will use descriptive statistics and general linear mixed models to test the hypotheses. Both intervention and control group participants will each receive $120 for their time during data collection visits ($35 at Time 1, $40 at Time 2, $45 at Time 3) and $5 to help with transportation costs each time they come to class or data collection visit.

Participants in the intervention group will receive a 12-week Intensive Intervention (Phase I) with weekly 2-hour sessions consisting of 60 minutes of nutrition and exercise education and coping skills training, a 45-minute physical activity class, and 15-minute stress management session. During Continued Support (Phase II), participants will meet monthly for 3 months for 60 minutes of classroom discussion regarding problems they are having with nutrition and physical activity. Data collection in the wait-list control group will occur at the same time intervals as women in the intervention group. Following the last data collection, we will offer Phase I of the intervention to women in the wait-list control group.

Participants will be tracked using ID numbers. Designated research staff will collect, gather, and enter data into a REDCap database with built-in range checks and skip patterns. The Project Coordinator/Senior Research Assistant with double-check 20% of data entry against the raw data for quality assurance. Data will be verified and stored in a secure server. Data will undergo range, consistency, and outlier checks. All data decisions will be recorded in a logbook with an audit trail. SAS datasets will be created for analysis.

Risks to Human Subjects

The intervention requires that during the Intensive Intervention each woman in the intervention group attend 12 classes for 120 minutes. During Continued Support women will meet monthly for 3 months with their interventionists. The interventionist will weigh all women in a private area and provide feedback. The interventionist will then meet with the women for 60 minutes to discuss nutrition and exercise challenges. The women will then attend a 45 minute exercise session. The women will also be encouraged to exercise 30 to 60 minutes a day on most days of the week. Women in the wait-list control group will be offered the Intensive Intervention at the end of the 12-month follow-up.

As a part of the first data collection after women consent to enroll in the study, they will complete an interviewer-administered survey in their preferred language (English, Spanish). Women will have their height, weight, waist circumference, and blood pressured measured by a bilingual research assistant in a private room. Trained research assistants will also collect carotid-femoral pulse wave velocity measures, a blood sample by venipuncture, and a sample of hair for cortisol assessment. We are aware that adverse events may occur and an adverse event monitoring committee will monitor their occurrence and the overall risk of the study to participants. No more than minimal risks are anticipated from this study and these potential risks are related to the intervention, a breach of confidentiality, physical measures, and venipuncture. Women who express fatigue during sessions will be excused from the session and another time convenient for them will be scheduled to make up the content. If a woman expresses fatigue during data collection, the data collection session will be terminated immediately, and a follow-up appointment scheduled. It is not anticipated that the classes or data collection will cause any adverse effects, but participants will be encouraged to identify any concerns to the study staff. Identifying data will be kept separate from questionnaires and locked in the PI's filing cabinets and locked office. All participants will continue to receive routine medical care from their health care providers throughout the study. Referral to their health care provider will be made if any adverse effects are self-identified. There are no known social or legal risks for the women who consent to participate in this study.

Adequacy of Protection against Risks

Dr. Cortés has extensive experience working with Hispanic/Latino women and Co-Mentors/Co-Investigators, Drs. Berry and Perreira have strong relationships with the study sites. To assure that we meet enrollment targets**,** all project staff will be bilingual and all recruitment and intervention materials and instruments will be bilingual (English and Spanish). Two months before enrollment, the bilingual Project Coordinator will give a presentation to staff at community centers in two counties in North Carolina and place English and Spanish language flyers and brochures in each. The project coordinator will screen potential participants by phone. If a woman meets inclusion criteria and is interested in participating, we will schedule an appointment at a convenient time at the participant's home or community site to confirm eligibility and obtain informed consent. Written consent will be obtained by a bilingual research assistant using appropriate Informed Consent forms approved by the institutional review board of the University of North Carolina at Chapel Hill. Informed Consent forms will be available in English and Spanish. Potential participants are assured that participation is voluntary and that refusal to participate will not influence their health care or position in their community. All participants will be provided with instructions on how to contact the investigative team if any problems or concerns arise. Data will be collected only from subjects who have agreed to participate in the study. Consents will be stored in locked file cabinets in the research office, separate from any study data. All participants will be adults age 40-55 years.

Risks will be minimized by study procedures that safeguard privacy. Personal Identifying Health Information (PHI) will be stored on password-protected lap top computers, with only a subject study number as an identifier. The key linking participants' PHI to their data will be kept in a separate file on a secure server, and destroyed at the conclusion of the study. Data will be

recorded on forms on which the only identifier is a research ID code. Only the PI and project coordinator have access to the link between the research ID code and PHI. No names or identifying information will be included in research reports. Subjects' names will not appear on questionnaires. While data collectors are in the home, any previously completed surveys for data collection forms will be kept in a secure place, such as the trunk of a car, until they can be delivered to the research office for data entry where they will be kept in a locked file cabinet. Codes will be used to identify the nursing home and all individual subjects. All computers housing research data have passwords and timed screen savers requiring a password for access. All team members who have contact with data will complete training sessions on proper and secure ways to handle sensitive information and how to handle computing environments in general. In addition, no individually identifiable information will be included in disseminated findings; study results will be reported in aggregate only.

To minimize potential participant burden, (a) we have limited the total number of contact hours required in the intervention; (b) we will deliver the intervention in a space near the participants' home; c) physical activity sessions will be led by a bilingual physical activity interventionist certified by the American College of Sports Medicine; and (d) we will complete data collection at the participants' home and provide incentives. If any participant has a physical injury, we will help them seek immediate medical attention. If at any time any participant voices concern to the study staff that they are fatigued or do not want to continue, they will be encouraged to stop and return to the next class.

Potential risks of the physical measures, venipuncture, and hair cortisol along with specific strategies for minimizing risk, will be discussed with each participant during the informed consent process and at each data collection period. Risks will be minimized by using bilingual trained RAs, a standardized protocol, and phlebotomists who follow proper technique. Provision for medical treatment, should it be required, is included in the written informed consent; each patient receives a copy. Women can stop at any time or refuse to complete any measure and that will not affect their ability to continue in the study.

2.3.2 KNOWN POTENTIAL BENEFITS

Potential Benefits of the Proposed Research to Human Subjects and Others
Participants. Participants have the potential to benefit from improved CVD risk awareness and health behaviors (e.g., nutrition, physical activity, coping strategies, self-efficacy). They may receive some psychological benefit from stress management sessions and learning coping skills such as problem-solving. Participants may also benefit from the study my decreasing their biologic CVD risk (i.e., blood pressure, arterial stiffness, weight, waist circumference).

Others/Community. The proposed research has potential public health benefits because Hispanic/Latinos are the largest ethnic minority in the United States. Progress regarding CVD risk among perimenopausal Latinas may lead to significant improvement in the overall CVD burden in the US.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

See 2.3.1 above for assessment of potential risks and benefits

3 OBJECTIVES AND ENDPOINTS

Primary Objective: To examine the feasibility and initial efficacy of the multi-component behavioral intervention to reduce biologic CVD risk from Time 1 (baseline) to each of Time 2 (6 months) and Time 3 (12 months).

Secondary Objective: To evaluate the initial efficacy of the intervention to improve health behaviors, adiposity, inflammatory and stress biomarkers, and vasomotor symptoms from Time 1 (baseline) to each of Time 2 (6 months) and Time 3 (12 months).

Primary Outcomes:

- Systolic and diastolic blood pressure
- Carotid-femoral pulse wave velocity
- Total cholesterol
- High-density lipoprotein
- Low-density lipoprotein
- Triglycerides
- Fasting blood glucose
- Enrollment and retention rates
- Intervention attendance
- Participant satisfaction with the intervention and study protocol

Secondary Outcomes:

- Health behaviors (nutrition, physical activity, sleep)
- Self-efficacy (eating and exercise)
- Adiposity (weight, body mass index, waist circumference)
- High-sensitivity C-reactive protein
- Hair cortisol

Other Outcomes:

- Vasomotor symptoms

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study will use a cluster randomized repeated measures study design with two groups to evaluate the feasibility and initial efficacy of the intervention with 80 perimenopausal Latinas. The intervention group (n=40) will receive a 3-phased intervention. In Phase I (Intensive Intervention), bilingual community health workers will meet with women in small groups to deliver 12 weekly (3 months) 2-hour sessions including education, group physical activity, stress management, and coping skills training. Phase II (Continued Support) consists of 3 monthly 1-hour sessions led by community health workers to problem-solve issues related to nutrition and exercise, stress management, and to provide feedback and support. During Phase III (Follow-up), participants are expected to maintain skills on their own for 6 months. Data will be collected at baseline (Time 1), completion of Phase II (Time 2, 6 months after baseline), and after completion of 6 months on their own (Time 3, 12 months after baseline). Data in the wait-list control group (n=40) will be collected at the same time intervals as the intervention group. After Time 3 data collection, they will be offered the Intensive Intervention (12 weekly sessions). Both groups will receive reminders a week prior to each data collection visit and a monthly "thank you" card for their continued participation.

Data will be collected at Time 1 (0 months [baseline]), Time 2 (6 months [completion of the intervention]) and Time 3 (12 months [after 6 months with no contact from the study staff]). Time 2 data will determine the magnitude of the intervention effects after the intensive intervention and continued support; Time 3 data collection will test initial efficacy after participants have had sufficient time to implement their new nutrition, physical activity, and coping skills on their own. We will assess feasibility using questionnaires at Time 3, as well as process evaluations and attendance logs. We chose these times because 6-to-12 months after completion of an intervention is a standard interval for follow-up in behavioral interventions during perimenopause [34].

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Preliminary studies have demonstrated that perimenopause is an important time to implement behavioral interventions for the prevention of CVD. While behavioral interventions have been shown to increase CVD risk awareness and knowledge of heart-healthy behaviors (e.g., diet and exercise) among Hispanics/Latinos [31,32], most interventions among Latinas have been education only with either a short follow-up (<6 months) [31] or no assessment of biologic CVD risk [33]. Additionally, although studies among non-Hispanic White and Black women have shown that dietary and physical activity interventions can slow the progression of subclinical atherosclerosis during perimenopause [35], no such interventions have focused on perimenopausal Latinas. Our study will address important limitations of prior interventions. We will pilot test a novel multi-component behavioral intervention integrating evidence-based education - *SCSV* curriculum [36] - with coping skills training developed and tested by Co-Investigator Dr. Berry [37], physical activity sessions, and stress management. Thus, this is a

novel multi-component intervention to reduce biologic CVD risk (blood pressure, arterial stiffness, lipids, blood glucose) and to improve health behaviors (nutrition, physical activity, sleep, coping strategies, self-efficacy, stress management) among perimenopausal Latinas.

4.3 JUSTIFICATION FOR INTERVENTION

Risk of CVD increases substantially during perimenopause. Perimenopausal Latinas remain considerably less likely than non-Hispanic White women to meet physical activity and dietary guidelines, or be aware that CVD is the leading cause of death among women. In North Carolina and throughout the US Latinas often live in a sociocultural environment of poverty, have limited English proficiency, and face social isolation and discrimination [37]. Latinas often reside in built environments that may further contribute to CVD risk due to limited access to affordable healthy food options and safe public spaces for physical activities [38]. We will collect data on the sociocultural and built environment to tailor the intervention, and intervene on the behavioral influences of cardiovascular health (i.e., nutrition, physical activity, sleep, stress management, coping strategies and self-efficacy) to decrease biologic CVD risk among perimenopausal Latinas. Community health worker-led behavioral interventions among Latinos have been successful in improving health behaviors [31,32], although reduction of biologic CVD risk has been inconsistent [31,39]. Importantly, prior interventions have not targeted perimenopausal Latinas specifically or examined arterial stiffness, an independent predictor of CVD events [29]. Furthermore, these interventions have not incorporated physical activity, stress management, and coping strategies, essential components to reduce CVD risk among perimenopausal Latinas. To address these deficits, this 12-month multi-component behavioral intervention integrates evidence-based education and coping skills training with physical activity and stress management to **1)** reduce biologic CVD risk, including arterial stiffness; and 2) improve secondary outcomes of health behaviors, adiposity, inflammatory and stress biomarkers, and vasomotor symptoms.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if she has completed Time 1 (baseline), Time 2 (6 months) and Time 3 (12 months) data collection.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Inclusion criteria are: age 40-55 years; self-identify as Latina; understand spoken English or Spanish; perimenopausal based upon the Study of Women's Health study definitions [40]: menstrual bleeding in the past three months, but timing of periods have varied in past year, or no menstrual bleeding in the past 3-11 months; intact uterus and at least one ovary; not currently pregnant; no hormone therapy or oral contraceptives in the past three months (as these may alter bleeding patterns). These eligibility criteria are consistent with previous observational studies and clinical trials in perimenopausal women [41] and are standard to clearly assess menopausal status in midlife women.

5.2 EXCLUSION CRITERIA

Exclusion criteria are: history of CVD (heart attack, stroke, coronary heart disease), impaired physical mobility, or difficulty exercising. Women will not be excluded if on current anti-hypertensive, lipid-lowering, or diabetes medications.

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures will not be consented or enrolled in the study. We will keep track of screen failures and reasons why they failed to meet inclusion criteria.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Procedures for Minority Recruitment and Enrollment and Challenges
This study builds on established partnerships between UNC-CH, local churches, and community centers in Orange County and Durham County. Dr. Diane Berry and Dr. Krista Perreira have extensive experience working with these communities in prior studies, and will guide my community engagement. To assure that we meet enrollment targets**,** all project staff will be bilingual (English, Spanish) and all study materials (recruitment, intervention, and instruments) will be available in Spanish. Participants will be recruited by a Community Health Worker (CHW) and Research Assistant (RA) from local churches, and community centers in Orange County and Durham County. Two months before enrollment, the Project Coordinator will meet with staff at the churches and community centers to confirm recruitment strategies and place Spanish language flyers with information about the study and eligibility criteria in the entrance and common areas. The flyers will contain a phone number for individuals to call if they’re interested in participating in the study. Additionally, the CHW and RA will be available weekly after church services and monthly at events organized by community centers. RAs will record the names and

telephone numbers of interested women privately and schedule them for a phone screening. This approach worked well in prior studies that enrolled 56 women in over a month [42]. We plan to enroll 8-10 women per week and can extend the timeline for enrollment if needed. If we have difficulty enrolling participants we will ask community leaders from the recruitment sites for advice. The Project Coordinator will conduct a phone screening, asking women for their birthdate, last menstrual period, regularity of menstrual periods, history of hysterectomy or oophorectomy, use of hormone therapy or birth control pills, and history of CVD. Women who meet the study criteria will be scheduled for a baseline visit to confirm eligibility, review the study, requirements of participants, and the risks and benefits of participating, random assignment and answer questions. Data collection will occur in a private location in the participant's home (approximately 90 minutes). We have time in the schedule for make-up data collections.

Procedures for Minority Retention and Challenges

To strengthen retention, our intervention sessions will be interactive, with culturally-tailored content developed to engage and sustain participants' interest (*Su Corazón, Su Vida* curriculum and coping skill training). Women who miss a learning session will be offered an opportunity to review the weekly class content over the phone, and will be reminded when the next class will be held. We will provide women with handouts including tips, a list of resources, recipes, and illustrations in Spanish on how to improve their nutrition, physical activity, and sleep. We will ask participants for phone numbers of family members and permission to call them if we cannot contact them. We will be flexible in scheduling enrollment and data collection appointments and send thank you cards. We will remind participants of their data collection visits one week before and confirm the day before the appointment. Participants in both groups will receive $35 after the baseline visit, $40 after the 6-month visit, and $45 after the 12-month data collection. These approaches have been successful in prior studies with Latinas, with <20% attrition [43]. We will make every effort to keep our attrition lower than 20%; if attrition exceeds 20%, we will contact the participants to ask why they stopped coming and develop strategies to assist them to continue in the study if they wish. We will also meet with our Community Advisory Board to develop and implement strategies to improve retention.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Intensive Intervention
The intensive intervention consists of 12 weekly bilingual (English, Spanish) sessions that include 60 minutes of interactive learning, 45 minutes of physical activity, and a 15-minute stress management session. The first 8 sessions will integrate education from *SCSV* related to CVD risk awareness, healthy food choices, physical activity, blood pressure control, and diabetes. To enhance the relevance of the curriculum to perimenopause, we will include messages from American Heart Association Go Red Por Tu Corazón. Each week CHWs will give participants a SCSV or AHA Go Red Por Tu Corazón handout with information on healthier meals and increasing daily physical activity. In the remaining four learning sessions of Phase I, we will integrate previously tested and acceptable coping skills training sessions (i.e., goal-setting, problem-solving, cognitive restructuring, conflict resolution, assertiveness training) with a focus on barriers for perimenopausal Latinas. Trained bilingual CHWs will deliver learning sessions and 15-minute stress management sessions in groups of 20 participants.

Physical activity classes will be held for 45 minutes after the intensive intervention classes and will include a warm-up and then activities such as Zumba, Kick Boxing, walking, use of light weights and stretch bands, and a cool-down. A bilingual physical activity interventionist certified by the American College of Sports Medicine will teach the physical activity classes and reinforce ways to increase physical activity and decrease sedentary behaviors. At baseline, we will give participants an accelerometer and the RA will train them in its use as part of the intervention. The intervention group will be encouraged to increase their physical activity weekly by small increments until they are averaging 10,000 steps a day or 150 minutes per week; this group will also be provided information on the sociocultural and built environments such as a list of grocers where they can access healthy affordable food and free or low-cost spaces to exercise (e.g., YWCA/YMCA) close to home. Missed physical activity sessions will not be made up, but participants can make up learning and stress management sessions.

Continued Support
During Continued Support, participants will return to the church for classes once a month for 3 months. As a part of the intervention, participants engage in a discussion run by the bilingual CHW, who will help women solve problems they have encountered related to nutrition and physical activity for 60 minutes and then receive a 45 minute physical activity class and 15-minute stress management session. If a participant misses a class, the bilingual interventionist will call and ask how the woman doing and give the date of the next class. Continued support classes will not be made up.

Wait-List Control Group
Data will be collected from the wait-liste control group at Time 1, Time 2, and Time 3; and participants will receive up to $120 for their participations ($35 at Time 1, $40 at Time 2, and $45 at Time 3) in addition to a $5 transportation voucher at each data collection. The wait-list control group will receive a "thank you" postcard for their continued participation. Participants will receive a accelerometer and log book after they have completed Time 3 data. At that time, the wait-list control group (the cluster) will also be offered the intervention classes in the church. In addition the monthly "thank you" cards, participants will be called several days before classes and data collection to remind them.

6.1.2 ADMINISTRATION AND/OR DOSING

See 6.1.1 for details

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Fidelity of the Intervention
We have structured the fidelity of the intervention using the NIH five category Treatment Fidelity Framework [44]. For category one, **treatment design**, the intervention and control group condition is clearly defined and participants will receive the same duration of contact over time. The CHWs will have experience teaching health interventions, and the theoretical model is clearly articulated. For category two, **training**, The bilingual interventionists will be trained by the PI using a standardized manual and teach back the intervention to the PI. For category three, **delivery**, the bilingual project coordinator will observe two randomly selected sessions per month using a checklist to score delivery based on pre-identified content. We define fidelity as delivering >80% of the protocol content. If drift occurs, the PI will retrain CHWs until the protocol is followed consistently. CHWs will collect data on attendance, reasons for absence, and make-up learning sessions provided. For category four, **receipt**, interventionists will ask questions and generate discussion during each learning sessions to assess the degree to which participants understand the content and participants will be asked to set a goal based on the information reviewed during the learning session. CHWs will evaluate category five, **enactment,** during the 3 monthly continued support sessions by discussing changes in diet, physical activity, number of steps taken per day, and stress management; RAs will also assess enactment during exit interviews at Time 3 with participants.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

After enrollment and baseline assessment, the two churches will be randomized to either the intervention or wait-list control group using a computer-generated randomization table. Participants will be informed of their group assignment by telephone. Data collection research assistants will be blinded to group status.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

See 6.2.1 for details

6.5 CONCOMITANT THERAPY

N/A

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

The intervention will only be discontinued after consultation with the study team and the program officer.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue a participant from the study for lost-to-follow up and unable to contact subject.

The reason for participant discontinuation or withdrawal from the study will be recorded. Participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if she fails to return for scheduled visits and study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to return for a required study visit:

The site will attempt to contact the participant, reschedule the missed visit, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls). These contact attempts will be documented in the participant's study file.

Should the participant continue to be unreachable, she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Summary of Variables, Measurement, and Data Collection Time Points			
Variables and Measurement	**0**	**6**	**12**
Feasibility			
*Process evaluation checklist (bi-monthly)	--	--	--
*Screening and enrollment logs	X	X	X
*Intervention attendance	X	X	X
*Data collection attendance	X	X	X
Exit interview			X
Biological CVD Risk Factors (Primary Outcomes)			
Systolic and diastolic blood pressure	X	X	X
Fasting blood glucose	X		X
Fasting lipid profile	X		X
Arterial stiffness (carotid-femoral PWV)	X		X
	X		X
Health Behavior (Secondary Outcomes)			
Nutrition and food security	X	X	X
Physical activity questionnaire	X	X	X
Accelerometer (7 days, 24 hours/day)	X	X	X
Sleep questionnaire	X	X	X
Perceived stress	X	X	X
Coping response inventory	X	X	X
Eating self-efficacy scale	X	X	X
Exercise self-efficacy scale	X	X	X
Biological Influences (Secondary Outcomes)			
Height, Weight, BMI	X	X	X
Waist Circumference	X	X	X
Hair Cortisol and Hs-CRP	X		X
Vasomotor symptoms questionnaire	X	X	X
Demographic, Sociocultural, and Environmental	X	X	X
Demographic questionnaire (e.g., age, education)			
Acculturation questionnaire (e.g., years in US)			
Everyday discrimination scale			
Brief resilience scale			
Health history questionnaire			
Reproductive history questionnaire			
Community food assessment			
Neighborhood risk assessment			
Physical activity resource assessment			

0 = baseline; 6 = 6-month (completion of intensive intervention and continued support); 12 = 12-month (after 6 months of maintenance on own); BMI = body mass index; Hs-CRP = high-sensitivity C-reactive protein; PVW = pulse wave velocity
*Completed by Project Manager

8.2 SAFETY ASSESSMENTS

N/A

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

Definition, Expected Risks, and Potential AEs. An adverse event (AE) is any untoward medical occurrence in a participant during the clinical study, which does not necessarily have a causal relationship with the intervention. An AE may include: 1) any new signs or symptoms; 2) any new illness or disease or deterioration of an existing condition; and 3) any clinically significant abnormal laboratory assessments or clinical tests. Additionally, per UNC-CH's policy all participant deaths, protocol deviations, complaints about the research, and breaches of confidentiality are reportable AEs. A serious adverse event (SAE) is any AE that results in one or more of the following outcomes: death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a serious medical event.

Identifying AEs. Potential risks identified for participants are outlined in the Protection of Human Participants section and will also be outlined in the IRB approved informed consent document. Participants will be queried about the occurrence of AEs at each visit. They will also be instructed to phone at any time during the study with an AE. The PI will work with the Safety Officer to develop a system to test whether abnormalities are equally distributedbetween the intervention and control groups. Data will be presented to the Safety Officer if a significant increase inabnormalities is noted. The Safety Officer will provide the PI with recommendations regarding problems that wouldrequire modification for safety reasons.

Reviewing and Reporting AEs. AEs will be reviewed by the Safety Officer and determined to be mild (no interference in usual activities); moderate (some interference in usual activities); or severe (usual activities were significantly interrupted). AEs will be categorized according to the likelihood that they are related to the study intervention. The Safety Officer will rate the assessment of attribution to the study as not related, unlikely, possible, probable, or definite to the intervention.

The PI will be responsible for ensuring that all AE and SAEs are reported to the Co-Mentors, scientific advisors, Senior RA, Safety Officer, the IRB and NIH/NIMHD within 3-7 days. An incident report will be created within 24 hours and sent by electronic email by the PI to the Co-Mentors, scientific advisors, Senior RA, Safety Officer, the IRB and NIH/NIMHD. The PI will follow-up with the participant and will prepare a report. The AEs will be reviewed every three months by the Co-Mentors, scientific advisors, the Senior RA, Safety Officer, and the PI, and a report prepared for the Human Participants Committee and the NIH/NIMHD. Process notes will be kept concerning any decisions.

Any SAE or deaths that occur during the study will be reported by telephone immediately to the Co-Mentors, scientific advisors, the Senior RA, Safety Officer, the IRB and NIH/NIMHD. An incident report will be sent by electronicmail by the PI to Co-Mentors, scientific advisors, the Senior RA, Safety Officer, the IRB and NIH/NIMHD within 24 hours. The PI will follow-up immediately with the participant to investigate and prepare a report for all members of theHuman Participants Committee and comply with all regulations regarding the reporting of SAEs. The PI will beresponsible for complying with all regulations concerning the reporting of a SAE and will prepare a full report forNIH/NIMHD. The PI will meet with the Co-Mentors, scientific advisors, and the Senior RA and seek input from the Program Officer. Process notes will be kept concerning any decisions.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

See 8.3.1 above

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

See 8.3.1 above

8.3.3.1 SEVERITY OF EVENT

See 8.3.1 above

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

Study Overview:
The overall goal of this project is to determine whether a multi-component intervention consisting of education and physical activity sessions, stress management, and coping skills training will decrease biologic cardiovascular risk (blood pressure, arterial stiffness, lipids, blood glucose) among perimenopausal Latinas. The DSMP outlined below will adhere to the protocol approved by The University of North Carolina at Chapel Hill (UNC-CH) Institutional Review Board (IRB) and the National Institutes of Health (NIH) and the National Institute of Minority Health and Health Disparities (NIMHD).

Monitoring Entity:
Principal Investigator (PI) and IRB. Oversight and monitoring of the conduct and progress of the study will be provided by the PI with delegation of responsibilities to designated study personnel, and the Institutional Review Board (IRB) of UNC. They will ensure all entry criteria are met prior to the initiation of the protocol and all study procedures and reporting of adverse events is performed according to the IRB-approved protocol. The PI will report adverse events to the Safety Officer, IRB, and funding agency.

Independent Safety Officer. We will appoint a Safety Officer with both clinical and intervention research expertise to provide quarterly safety monitoring throughout the conduct of the study. The Safety Officer will be independent from the study team. The Safety Officer will review the protocol, intervention components, and all data collection processes prior to study implementation. The Safety Officer will review interim data, all reports of adverse events quarterly, and, when necessary, issue recommendations to the PI regarding the continuation, modification, or termination.

Data Quality and Safety Review Plan and Monitoring:

Subject Accrual and Compliance with Inclusion/Exclusion. All data from participants screened for the study will be entered into the REDCap electronic study database. Designated research staff will collect, gather, and enter required data (written informed consent, Health Insurance Portability and Accountability Act (HIPAA) authorization, medical history and demographics) onto study data forms. Screened patients who do not meet study eligibility will have specific screening data entered into the study database. The collected data will be helpful in examining the patient population and feasibility of enrollment criteria and will include gender, age, race and reason for exclusion. All dates will be shifted and other Personal Health Information (PHI) will be removed from the study database upon study completion.

Participant Compliance to the Intervention. Data on compliance to the intervention will be collected weekly by the senior RA and reviewed quarterly by the Co-Mentors, scientific advisors, the Senior RA, Safety Officer, and PI. Compliance on the part of participants will be evaluated by attendance and process evaluation as outlined in the study. If intervention attendance drops below 80%, participants who have stopped coming will be called to ask for feedback. Using information gained from these phone interviews, the PI will schedule a meeting with the Co-mentors, scientific advisors, and the Safety Officer to discuss methods for improving compliance.

Study Visits and Data Collection. The PI and Dr. Crandell (Study Statistician) will oversee and train the senior RA to establish a system to ensure the verification of source data compliance. The source data will include original records necessary for the reconstruction and evaluation of the clinical trial. It will be clear who documented the data, documentation will be readable, signatures identifiable, concurrent, original copy, accurate and consistent, long-lasting and durable, available and accessible, complete, consistent, credible, and corroborated. All data will be first checked by two separate Research Assistants (RAs) at different times. Data entry and monitoring will be completed in REDCap, our Research Electronic Data Capture System. The PI has been trained in REDCap and has used it in previous studies and REDCap is supported by UNC-CH. Dr. Crandell will oversee the development of the REDCap database and train RAs how to compare data entry against source data and make corrections as needed. Dr. Crandell will develop a data dictionary to support accurate data entry between RAs and a data log book will be created to establish an audit trail for compliance.

Ongoing quality control procedures will be implemented for data collection, storage and processing. The senior RA will conduct monthly monitoring of the study database and generate

a report for the PI to review at team meetings. Standing agenda items for these meetings will include participant recruitment and retention, AEs, SAEs, protocol deviations, data integrity and overall study conduct.

8.3.3.3 EXPECTEDNESS

N/A

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The frequency of event assessment and follow-up for this study is summarized in the table below.

Frequency of Data Review		
Data Type	**Frequency of Review**	**Reviewer**
Subject accrual (including compliance with enrollment criteria)	Monthly	Co-Mentors, scientific advisors, the project coordinator, and Safety Officer
Status of enrolled subjects as of date of reporting	Quarterly	Co-Mentors, scientific advisors, the senior RA, and Safety Officer
Adherence data regarding study visits and intervention	Quarterly	Co-Mentors, scientific advisors, the senior RA, and Safety Officer
AEs and rates	Quarterly	Co-Mentors, scientific advisors, the senior RA, and Safety Officer

Safety Review Plan. Study progress and safety will be reviewed monthly. The PI will provide progress reports, including patient recruitment, attrition, and AEs to the Co-Mentors, scientific advisors, the senior RA, and Safety Officer following each of the monthly reviews. An Annual Report will be compiled including 1) a list and summary of AEs; 2) whether AE rates are consistent with pre-study assumptions; (3) reason for dropouts from the study; (4) whether all participants met enrollment criteria; (5) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (6) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the Co-Mentors, scientific advisors, the senior RA, and Safety Officer and forwarded to the IRB and NIH/NIMHD. The IRB will review progress of this study on an annual basis. The PI will also send copies of signed recommendations and comments from the Safety Officer to the NIMHD Program Officer within 1 month of each monitoring review.

Interim Analysis. The senior RA will generate semi-annual qualitative interim analysis reports on data obtained during phone call and returned end-of-study surveys to understand issues related to the uptake, usability, and adoption of this platform among this population. We will evaluate the screening and enrollment procedures, barriers to participation and retention, acceptability, technology problems encountered if any, and user feedback from the participants.

The information gained from this structured process will be used to both guide the refinement of the current protocol and to inform the design of a larger efficacy trial. **Stopping Rules.** There are no planned stopping rules for this study. **Protocol Modifications.** Modifications will not be undertaken without notification of the IRB, Safety Officer, and NIMHD Program Officer.

8.3.5 ADVERSE EVENT REPORTING

See 8.3.1, 8.3.3.2, and 8.3.4 above

8.3.6 SERIOUS ADVERSE EVENT REPORTING

See 8.3.1, 8.3.3.2, and 8.3.4 above

8.3.7 REPORTING EVENTS TO PARTICIPANTS

See 8.3.1, 8.3.3.2, and 8.3.4 above

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

If a woman becomes pregnant while she is in the study she will be withdrawn and follow-up ensured with her health care provider.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

See 8.3.1, 8.3.3.2, and 8.3.4 above.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

See 8.3.1, 8.3.3.2, and 8.3.4 above.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Aim 1: To examine the feasibility of the multi-component behavioral intervention. We will assess enrollment and retention rates; barriers and facilitators to enrollment; intervention fidelity; suitability of study procedures and outcome measures; and participant satisfaction with the intervention and study protocol.

Aim 2: To evaluate the initial efficacy of the intervention by comparing an intervention group to a wait-list control group (n=80; 40 per group) in a pilot study to a) decrease the primary outcomes of biologic CVD risk factors (blood pressure [BP], arterial stiffness, lipids, blood glucose); b) improve secondary outcomes (health behaviors: nutrition, physical activity, sleep, coping strategies) and other biological factors related to CVD risk (adiposity, inflammatory and stress biomarkers, vasomotor symptoms) from Time 1 (baseline) to Time 2 (6 months) and Time 3 (12 months).

Hypotheses and Statistical Considerations: This pilot study will descriptively assess the feasibility and validity of the cluster randomized controlled trial plan and is not expected to test the hypotheses of the main clinical trial.

We expect that on average, the intervention group will have a slower progression or a decrease in BP, arterial stiffness, lipids, and blood glucose compared to the wait-list control from Time 1 (baseline) to Time 2 (6 months) and Time 3 (12 months).

We expect the intervention group will show improvements in health behaviors (nutrition, physical activity, sleep, coping strategies, self0efficacy), adiposity, inflammatory and stress biomarkers, and vasomotor symptoms from Time 1 (baseline) to Time 2 (6 months) and Time 3 (12 months).

9.2 SAMPLE SIZE DETERMINATION

Sample size will be limited by available resources. Prior clinical trials among Latinas in North Carolina have enrolled 80-184 women successfully with <20% attrition [45]; therefore, enrollment of 80 women is realistic and achievable. Prior interventions in stress management [46] and exercise plus nutrition education [47] observed a change in systolic BP of 6mmHg (SD±11); our sample of 80 participants will yield 70% power to detect a change this large. This pilot study is effectively a cluster-randomized trial with two groups. Because we have two groups, the pilot is not sufficient for the estimation of intraclass correlation of change in outcomes, so we do not use traditional analysis methods for cluster-randomized trials. We can however, use baseline data to estimate potential variability between clusters, which will be helpful in the estimation of the number of clusters/cluster size required for the fully-powered clinical trial.

9.3 POPULATIONS FOR ANALYSES

Means, standard deviations, minimums, medians, and maximums will be determined for each continuous variable; frequencies and percentages will be tabulated for each categorical variable. Preliminary analyses will be performed to determine whether, despite randomization, the intervention and control groups were unbalanced on age, education, income, or other participant characteristics. Any variable with an imbalance between the groups at baseline will be examined to determine whether it is related to any of the outcome variables. If significant relationships are identified, the variable will be included as a covariate in the models for the affected outcome(s) as a potential confounder. An intent-to-treat analysis will be used in which all subjects are included in the analysis and analyzed according to their initial randomized assignment.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Aim 1. Using descriptive statistics (e.g., frequency, percentage, means, SDs), we will summarize enrollment and retention rates, and proportion of intervention sessions the participants attended. We will measure fidelity of the intervention (³80% attendance; delivery of >80% of content) using the process evaluation guide, and assess participant satisfaction with the study and the intervention using the exit interview.

Aim 2. We will use an intent-to-treat approach. Because random assignment is by group and not individually, we will examine potential systematic differences closely between the two groups, comparing baseline characteristics using the Student's t-test or Mann-Whitney test for continuous variables and Chi-square or Fisher's exact test for categorical variables. We will assess change in primary and secondary outcomes in the intervention and control group using using the Student's t-test or Mann-Whitney test for continuous variables and Chi-square or Fisher's exact test for categorical variables.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

See 9.4.1

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

See 9.4.1

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

The outcomes of most feasibility and pilot studies are measured with descriptive statistics, qualitative analysis, and the compilation of basic data related to administrative and physical infrastructure. At baseline we will determine means, standard deviations, minimums, medians, and maximums for each continuous variable; frequencies and percentages will be tabulated for each categorical variable.

9.4.6 PLANNED INTERIM ANALYSES

As discussed in 9.4.1., we will analyze the effect of the intervention on change biologic CVD risk factors (i.e., blood pressure, weight, was it circumference, BMI), and health behaviors from baseline to Time 2 (6 months [completion of the intervention]).

9.4.7 SUB-GROUP ANALYSES

See 9.4.1

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

See 9.4.1

9.4.9 EXPLORATORY ANALYSES

See 9.4.1

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

See human subjects section above for details of consent.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

See human subjects section above for details of consent.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

See human subjects section above for details of consent.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

At the completion of four years or 48 months the study will be closed unless a no cost extension is needed.

10.1.3 CONFIDENTIALITY AND PRIVACY

See Human Subjects above.

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator for the participants in this study.

The study participant's contact information will be securely stored at the site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored on REDCap. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of North Carolina at Chapel Hill School of Nursing.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies

It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in *45 CFR Part 75.303(a)* and *NIHGPS Chapter 8.3*, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the University of North Carolina School of Nursing. After the study is completed, the de-identified, archived data will be transmitted to and stored at the University of North Carolina School of Nursing, for use by other researchers including those outside of the study. We will not store any biological specimens.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor or Independent Safety Monitor**
Dr. Yamnia I. Cortés	Dr. Mary Lynn
The University of North Carolina at Chapel Hill	The University of North Carolina at Chapel Hill
Campus Box 7460	Campus Box 7460
919-966-5299	919-966-5450
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See DSMP Above

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Plan (DSMP) composed of individuals with the appropriate expertise. See the DSMP for details.

10.1.7 CLINICAL MONITORING

N/A

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Procedures will be followed according to standard protocols for height, weight, calculation of BMI, blood pressure, and collection of arterial stiffness measurements and questionnaire and accelerometer data.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed**.**

Source documents and the electronic data --- Data will be initially captured on source documents and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described above.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the Principal Investigator at the site under the supervision of the Project Manager. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by the University of North Carolina at Chapel Hill. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 5 years.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 5 years after the completion of the primary endpoint by contacting the Principal Investigator.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIMHD has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form

DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2.0	6-20-20	Procedures may be conducted virtually. In-person visits for data collection should be performed with proper facial covering and sanitizing. Prior to scheduling visits, research assistants must ask about COVID-19 symptoms and exposures (see attachment). During screening, participants will receive information about participating in a research study during COVID-19. 5.5., 6.0, 8.0	Changes are necessary to protect staff and participants from COIVD-19.

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