Local Protocol #: OSU-19152

ClinicalTrials.gov Identifier:

TITLE: Cool down with EMBr: Enhancing Menopausal Hot Flash Symptom Reduction after Breast Cancer

Principal Investigator:

Sagar Sardesai, MBBS MPH
Division of Medical Oncology
The Ohio State University Wexner Medical Center
B450 Starling Loving Hall
320 W 10th Avenue
Columbus, OH 43210
Tel: 614-293-6401
Email: Sagar.Sardesai@osumc.edu

Co-Investigators:

Bhuvaneswari Ramaswamy, MD, MRCP
Division of Medical Oncology
The Ohio State University Wexner Medical Center
B406 Starling Loving Hall
320 W 10th Ave
Columbus, OH 43210
Tel: 614-293-6401
Email: Bhuvaneswari.Ramaswamy@osumc.edu

Robert Wesolowski, MD
Division of Medical Oncology
The Ohio State University Wexner Medical Center
B401 Starling Loving Hall
320 W 10th Ave
Columbus, OH 43210
Tel: 614-366-8541
Email: Robert.Wesolowski@osumc.edu

Daniel Stover, MD
Division of Medical Oncology
The Ohio State University Wexner Medical Center
512 Biomedical Research Tower
460 W. 12th Avenue
Columbus, OH 43210
Tel: 614-685-6700
Email: Daniel.Stover@osumc.edu

Nicole Williams, MD
Division of Medical Oncology
The Ohio State University Wexner Medical Center
B405 Starling Loving Hall
320 W. 10th Avenue
Columbus, OH 43210
Tel: 614-293-3316
Email: Nicole.Williams@osumc.edu

Matthew Cherian, MBBS
Division of Medical Oncology
The Ohio State University Wexner Medical Center
Email: Matthew.Cherian@osumc.edu

Statistician: Patrick Schnell, PhD
College of Public Health
226 Cunz Hall
1841 Neil Ave.
Columbus, OH 43210
Tel: (614) 292-5274
Fax (614) 247-1846
Email: Schnell.31@osu.edu

Company: Embr Labs, Inc.
24 Roland St STE 102, Boston, MA 02129-1250

Pamela Peeke, MD, MPH
Chief Medical Officer, Embr Labs
Pam@embrlabs.com
301-407-0467

Matthew Smith
Chief Scientific Officer
Matt@embrlabs.com

Sonja Billes, PhD
Senior Scientific Advisor, Embr Labs
Sonja@embrlabs.com
503-896-0563

Interventions(s): EMBr Wave

Protocol Type:

Version #6.0 / Version Date: 3/14/2023
IRB Approved

Table of Contents

1.0 TRIAL SUMMARY & SCHEMA

Abbreviated Title	Embr Wave Study
Trial Phase	Feasibility
Clinical Indication	Patients with a breast cancer history experiencing bothersome hot flashes
Trial Type	Feasibility Pilot Trial
Type of control	Non-placebo controlled
Route of "administration"	Wrist, non-invasive wearable thermoelectric system
Trial Blinding	no
Treatment Groups	Two-arm, cross-over, non-placebo controlled trial
Number of trial subjects	50
Estimated enrollment period	12 months
Estimated duration of trial	Patients will not be followed after study termination
Duration of Participation	Approximately 8 weeks

1.1 Trial Design

This study is a randomized, crossover, non-placebo controlled trial of 50 patients with history of breast cancer and bothersome hot flashes. We propose to have 25 patients per arm in a two-arm study randomized to Embr Wave device vs no device or other treatment for bothersome hot flashes with a 1-month crossover. *The study has enrolled 23 participants with no active subjects in follow up as of 01/05/2022. The current amendment version dated 1/5/2022 includes the following changes a) update the study intervention to recently launched Embr Wave Generation 2 device and b) enroll an additional 10 participants so that approximately 50% of the study population will use the Generation 2 device. This increases initial planned sample size of n=40 by an additional 10 subjects to n=50. Study design shown below in Figure 1.*

1.2 Study Schema

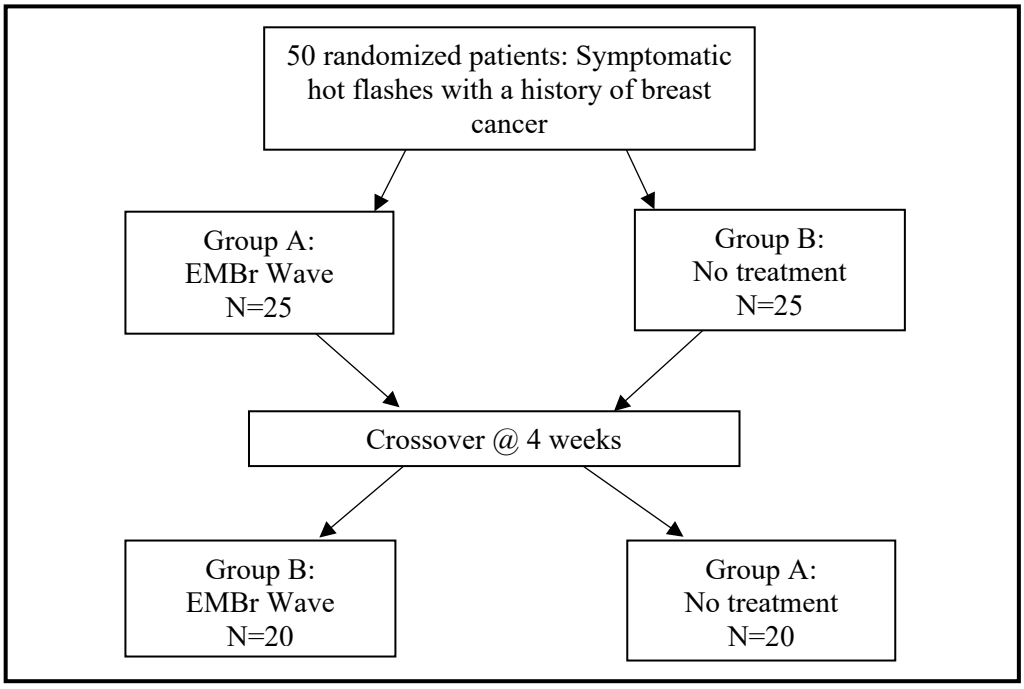

Figure 1: Study schema

2.0 TRIAL OBJECTIVES

This study will evaluate the preliminary efficacy of the EMBr Wave wrist device in managing the symptoms of hot flashes in patients with a history of breast cancer who have been experiencing hot flashes for at least 30 days prior to study entry. This study is based on published data that this device can improve thermal comfort by producing varying temperature pulses to counter uncomfortable sensations of heat or coolness.

1.1 Primary Objective

(1) To evaluate the feasibility of using EMBr Wave technology in women with a history of breast cancer who are experiencing bothersome hot flashes.

1.2 Secondary Objectives

(1) To evaluate the preliminary efficacy of EMBr Wave in reducing hot flash severity and frequency in women with a history of breast cancer.

(2) To identify in what ways EMBr Wave has the greatest potential efficacy, such as reduction in hot flash severity, frequency, duration, sense of control, or self-esteem.

(3) To estimate effect sizes to inform power calculations for a future Phase III trial

3.0 BACKGROUND

3.1 Bothersome Hot Flashes

At menopause, roughly 75% of women report bothersome hot flashes.[1] While the gold standard for hot flash relief is Hormone Replacement Therapy (HRT), this treatment is contraindicated for women with a history of, or active, breast cancer. Simultaneously, due to the negative impact of chemotherapeutics on remaining endogenous estradiol levels, and/or the induction an earlier menopause, breast cancer survivors often report more severe hot flash compared to women without breast cancer, negatively affecting their quality of life (QOL).[2]

3.2 EMBr Wave Device

While there are non-hormonal medical options to treat hot flash for breast cancer survivors, this study is investigating the use of a personalized cooling mechanism for hot flash relief. The EMBr Wave device has not previously been tested in clinical studies in breast cancer, but shows novel and promising hot flash relief for this unique population, possibly allowing for hot flash reduction without the use of an oral medication. The EMBr Wave device (both Generation 1 and 2) works by delivering heating or cooling pulses through the wirst bracelet. Because of the wrist's sensitivity to temperature, these pulses can be used to promote overall comfort despite other uncomfortable temperature senstions affecting the entire body. Users simply press either the cooling or heating button depending on which sensation they desire. The Generation 2 Embr Wave device has the same functionality as the Generation 1 device, but with an improved smaller design. A graphical design of the devices is showin in Figure 2.

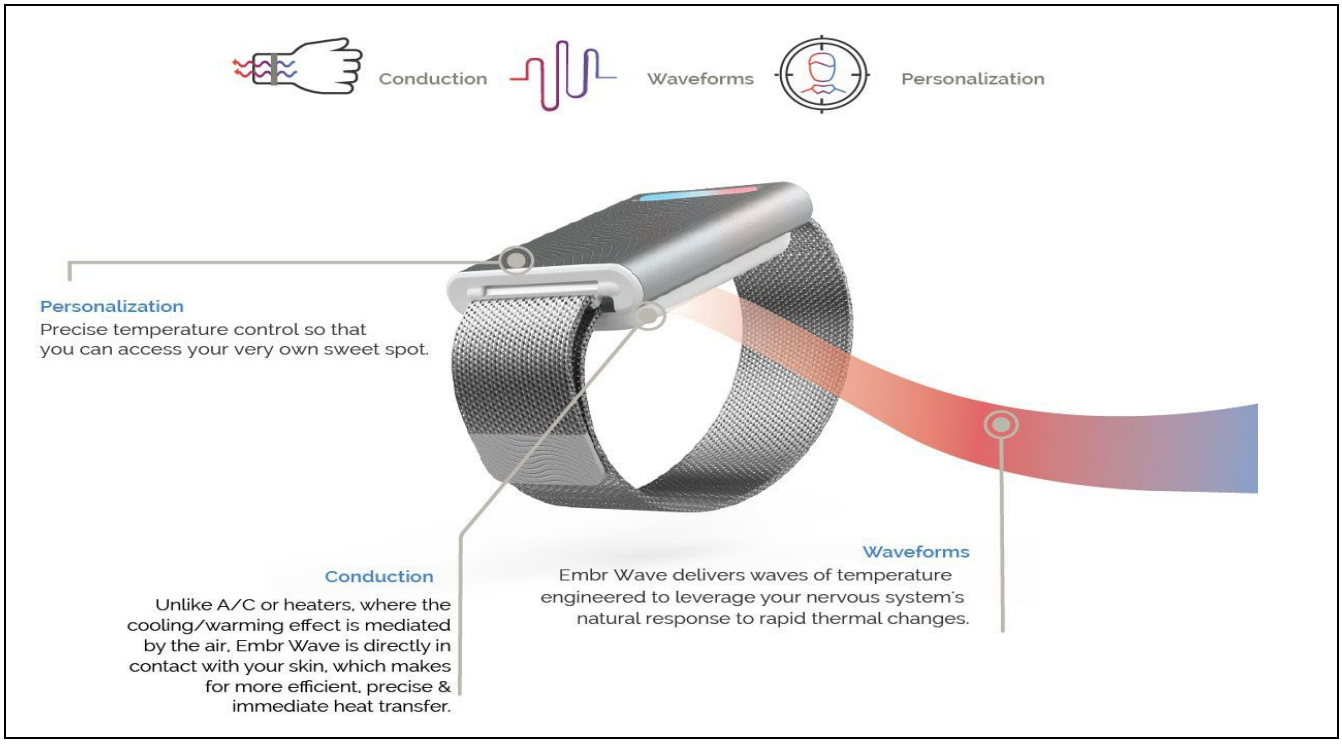

Figure 2: EMBr Wave Generation 1 Device (top) and Embr Wave Generation 2 Device (bottom)

3.3 Rationale and Feasibility

There are multiple side effects associated with breast cancer treatments, which are unable to be treated with traditional hot flash symptom management due to the contraindication of HRT in women who have been diagnosed with breast cancer. Safe and affordable strategies that may aid in the management of debilitating hot flashes are therefore needed. The overall objectives of this pilot trial are to evaluate a promising non-invasive intervention for treatment of hot flashes via EMBr Wave. If data from this pilot evaluation suggest that Embr Wave is beneficial, then more formal studies, with larger patient numbers, will be considered. Our goal is to leverage these results to secure additional funding, from grants or commercial partners, to support larger pilots and/or the development of new prototype devices.

4.0 METHODOLOGY

4.1 Entry Criteria

4.1.1 Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Age ≥ 18 years.
2. Women with history of breast cancer, DCIS, or LCIS (currently without evidence of malignant disease)
3. Bothersome hot flashes (defined by their occurrence of ≥ 28 times per week and of sufficient severityto prompt the patient to seek therapeutic intervention). Mean severity in a day should be >=4/10 on log scale of 0(none at all)-10(extremely).
4. Presence of hot flashes for >30 days prior to study entry
5. Ability to complete questionnaire(s) by themselves or with assistance.
6. Willingness to wear EMBr Wave device during the study period

7. Willingness to use the EMBr Wave mobile application
8. Have a working smartphone that can download the EMBr Wave mobile application (iPhone 6 or more recent generation, Android 8.0 or more recent generation)
9. ECOG Performance Status (PS) = 0, 1
10. Ability to provide informed written consent.
11. Life expectancy ≥6 months

4.1.2 Exclusion Criteria

Any of the following current (≤4 weeks prior) or planned therapies:

1. Antineoplastic chemotherapy (anti-HER2 agents allowed)
2. Androgens
3. Systemic estrogens. Local vaginal estrogen preparations are allowed, but need to have been initiated for vulvo-vaginal atrophy at least 28 days prior, and must not be expected to stop or change the dose or frequency of the medication during the study period.
4. Progestogens
5. Tamoxifen, raloxifene and aromatase inhibitors are allowed, and must not be expected to stop the medication during the study period
6. SSRIs/SNRIs, when being used for hot flash management or other indications such as depression, is allowed, assuming the dose will remain unchanged for the study duration
7. Gabapentin/pregabalin, is allowed, assuming the dose will remain unchanged for the study duration
8. Clonidine
9. Prior use of EMBr Wave.
10. Nickel allergy
11. Pregnant or nursing women since the safety of device has not been established in this population

4.2. Study Location and Sample

This study will be open for accrual at the Stefanie Spielman Comprehensive Breast Center and James Cancer Hospital. This trial will be conducted under the auspices of The Ohio State University. Testing will take place in clinics of the Stefanie Spielman Comprehensive Breast Center or done so virtually via phone and/or video calls. Patient eligibility will be determined according to the eligibility criteria listed. The study will enroll up to approximately 50 patients.

4.3 Registration and Randomization

Subjects who have given informed consent will be registered by the research coordinator and given a study number. Subjects will then be randomized via block randomization with random block sizes by the study coordinator following a randomization schedule produced by the statistician. Randomization will not be stratified.

4.4 Hot Flash Assessments

This pilot trial will be conducted to get an initial reading as to the potential benefit of EMBr Wave for diminishing distress caused by hot flashes. We do not expect that this instrument will

actually decrease the number of hot flashes. However, it might decrease hot flash severity and decrease the interference of hot flashes on patients' lives. The main instrument to determine the amount that hot flashes are interfering with patients' lives is by using a validated instrument called the Hot Flash-Related Daily Interference Scale (HFRDIS).[3]

Additionally, we will follow daily hot flash numbers and severities. The hot flash number and severity will be measured by the Daily Hot Flash Score,[4] which is a composite entity of both frequency and severity of hot flashes. The Daily Hot Flash Score is computed by the grade of severity multiplying the frequency of the same grade hot flashes according to the hot flash diary over a 24 hour period.

The OCEAN survey will also be administered to the participant to complete at baseline. This survey assesses the participant's personal connectedness that they have with their body and to the world around them. This survey gives perspective to the information obtained from the participant while they are using the EMBr Wave.

Patients will also be given instructions on how to sync their EMBr Wave with the EMBr Wave mobile application once a day, which will allow us to collect usage data from the devices. This will be used to further understand technology adoption over the 4 weeks that patients are using EMBr Wave during study participation.

We will also evaluate patient satisfaction with device use at the end of treatment using a 10-point Likert scale and through answering several Likert-type questions related to perceived device efficacy. These items will include assessment of the ways EMBr Wave had the greatest potential efficacy, such as reduction in hot flash severity, frequency, duration, sense of control, or self-esteem, as well as device usage.

The HFRDIS, Daily Hot Flash Score, and OCEAN survey will be administered on paper or virtually via RedCap survey distribution at baseline. Participants will be given paper Daily Hot Flash Score sheets for their own use. For study data collection, electronic surveys will be sent by email via Research Electronic Data Capture (REDCap) for daily and weekly hot flash assessments and the post-treatment satisfaction and efficacy questionnaires. Survey reminder emails and phone calls from study team will be sent to participants for incomplete HFRDIS surveys and satisfaction and efficacy assessments. If a participant initiated the daily surveys on paper prior to the study team using electronic data collection, she will continue using paper assessments for the duration of the study. If assessments are incomplete at end of intervention, the study coordinator will utilize paper forms to collect assessments, as appropriate.

Virtual enrollment will be presented as an option to eligible participants. In this option, calls (phone and/or video) will be done between the research coordinator and participant to discuss the study; screen for eligibility; discuss the informed consent and how to sign it; orient the patient to the device and associated smart phone application; and discuss how to return the device at the conclusion of the device usage. The informed consent document will be sent to the participant to sign via email or mail to obtain a pen signature after the participant has verbally agreed to participate in the study during the call. In addition to either receiving the signed informed consent form via email or mail, the participant will also be able to email the full picture of their signed informed consent form to the study coordinator's email and this will serve as a third option of informed consent documentation. After the consent document is signed, randomization will be done and the research coordinator will then inform the patient the

next steps depending upon their group assignment. When it is time for the participant to wear the device, it will be mailed to them via a secure and reliable address. An orientation call will be conducted when the device is received and will be worn starting the day of their designated month. The device will be returned at the end of this said month. For the orientation call, the participants will be sent an instructional packet to reference and discuss. These participants that enroll virtually will also complete the surveys electronically via RedCap. The EMBr device will be mailed in safe and secure packaging for transit.
The OSUCCC Recruitment, Intervention and Survey Shared Resource (RISSR) will be utilized to administer electronic data collection for assessments. REDCap (Research Electronic Data Capture) provides a secure, web-based application that is flexible enough to be used for a variety of types of research, provides an intuitive interface for users to enter data and has real time validation rules (with automated data type and range checks) at the time of entry. Data are maintained behind the OSUMC firewall, and REDCap is 21 CRF Part 11 capable. It offers easy data manipulation with audit trails and ad hoc reporting functionality for reporting, monitoring and querying patient records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

4.5 Study Intervention

EMBr Wave devices will be worn by study participants during the daytme and nighttime during the treatment periods of the trial. Participants will be asked to use the device as needed during the daytime and nighttime for management of hot flashes and night sweats. Participants will be asked to complete the hot flash assessments described above. Because hot flashes are transient and the EMBr Wave device is not expected to modify the underlying condition, a carry-over effect is unlikely in the crossover design. Due to the unlikeliness of carry-over and to avoid unnecessarily increasing patient burden, we will not use a wash-out period.

4.6 Clinical Assessment

Participants will be evaluated for hot flashes prior to initiation of the study. For participants enrolled to the study, the study team will abstract from the electronic medical record: clinical characteristics (cancer type, stage, receptor status), treatment history (surgery, radiation therapy, chemotherapy, endocrine therapy) and associated dates, and medications that affect or treat hot flashes. Chart abstraction will include the use of antidepressant medications since these drugs may have an effect on hot flashes.

4.7 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Loss of device greater than one time

4.8 Duration of Follow up

Patients will not be followed after eight weeks. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

4.9 Criteria for Removal from Study

The following criteria will be used for removal of patients from the study: (1) patient withdraws their participation; (2) patient has a disease progression or dies (whichever occurs first); (3) the study is terminated by the Principal Investigator; The reason for study removal and the date the patient is removed must be documented in the Case Report Form.

4.10 Adherence

Because of the limited anticipated adverse effects from the device and the ease of wearing the device, we anticipate excellent adherence. Devise usage will be electronically tracked through the study. Lost devices will be replaced once and if recurred, will be removed from study.

5.0 POTENTIAL TOXICITY, DOSE MODIFICATIONS, AND MANAGEMENT

Because EMBr Wave is a superficial, non-invasive device, we expect to see very little or no toxicities at all that are seen in its chronic use. Regardless, we will monitor for them. The severity of adverse reactions is categorized from grade 1 to grade 5 in increasing severity.

Table 4. General descriptors for the toxicity grades, ranged from mild to fatal.

Grade 1	Mild – the adverse reaction does not interfere in a significant manner with the subject's normal functioning level. It may be an annoyance.
Grade 2	Moderate – the adverse reaction produces some impairment of functioning but is not hazardous to health. It is uncomfortable and/or an embarrassment
Grade 3	Severe – the adverse reaction produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health
Grade 4	Severe – adverse reactions that include or lead to either a) a life-threatening event, though acute and without permanent effect, b) prolonged inability to resume usual life pattern, or c) impairment of ability to adequately deal with future medical problems
Grade 5	Death related to AE

Toxicity will be monitored during study visits and telephone calls using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE) of the National Cancer Institute will be used:

(https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf). Grade 3, 4 and 5 toxicities that are related to the study will be reported as adverse events.

Patients with Grade 3-4 adverse reactions that are related to the study will be removed from the study.

7.0 TREATMENT PLAN

7.1 Treatment Plan and Overview

Eligible patients will be approached by study personnel in the clinics at Stefanie Spielman Comprehensive Breast Center, the James Cancer Hospital, and the Center for Women's Health at the Ohio State University Wexner Medical Center. The person obtaining informed consent will tell the patient that 1) participation is voluntary, 2) participation or non-participation will not affect their usual care and management, and 3) patient confidentiality will be maintained in the event that the results of the study are published. The potential toxicities associated with EMBr Wave will be explained fully to the patient. Patients will be provided with a consent form to review, and all questions will be answered. After the signed informed consent has been obtained, a study identification number will be assigned to the patient for use on all data collection forms and samples. Medications and supplements will be reviewed with participants. Research team members may periodically call participants on the phone to remind them to complete the study surveys and to see if the participants are having any problems with the watch.

7.2 Study Calendar

Informed consent, randomization		
	Group A	**Group B**
Day 0	• Receive EMBr Wave • EMBr Wave orientation with introduction to device and mobile application • HFRDIS questionnaire • Daily Hot Flash Score • OCEAN psychographic survey	• HFRDIS questionnaire • Daily Hot Flash Score • OCEAN psychographic survey
Days 1–28	• Daily Hot Flash Score • Device usage assessment	• Daily Hot Flash Score
Days 7, 14, 21, 28	• HFRDIS questionnaire	• HFRDIS questionnaire
Day 28	• Return EMBr Wave • Patient satisfaction / perceived efficacy assessment	• Receive EMBr Wave • EMBr Wave orientation with introduction to device and mobile application
Days 29–56	• Daily Hot Flash Score	• Daily Hot Flash Score • Device usage assessment
Days 35, 42, 49, 56	• HFRDIS questionnaire	• HFRDIS questionnaire
Day 56		• Return EMBr Wave

		• Patient satisfaction / perceived efficacy assessment

In addition, patients will record their Daily Hot Flash Score daily in their journals.

9.0 ADVERSE EVENT REPORTING

Adverse event: Any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure; also an "unanticipated problem" of any nature (e.g., psychological or social harm) (designated as unrelated, definitely related, probably related, or possibly related; see below)

Serious adverse event: Any adverse event that is fatal or life threatening, is permanently disabling, requires inpatient hospitalization or prolongs hospitalization, or results in a congenital anomaly or birth defect.

Life-threatening event: Any adverse event in which the subject is at immediate risk of death from the reaction as it occurs; does not include a reaction that, if it were to occur in a more serious form, might cause death

Unexpected event: Any adverse event that is not identified in nature, severity, or frequency in the investigator brochure, study protocol, consent form, or IND application; or the event was more serious than anticipated.

9.1 Attribution of the Adverse Events

Definite: AE is CLEARLY RELATED to the study treatment.
Probable: AE is LIKELY RELATED to the study treatment.
Possible: AE MAY BE RELATED to the study treatment.
Unlikely: AE is DOUBTFULLY RELATED to the study treatment.
Unrelated: AE is CLEARLY NOT related to the study treatment

9.2 Documentation

CTCAE version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

For expedited reporting purposes only:

- AEs for the agent that are bold and italicized in the CAEPR (i.e., those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

All adverse events must be documented in detail within the medical record. The patient will be observed and monitored carefully until the condition resolves, stabilizes, or its cause is identified. All adverse events, including laboratory abnormalities, will be followed up according to good medical practices. Information to be recorded includes the following:

1. Specific type of reaction.
2. Duration of reaction.
3. Severity/grade of reaction according to the NCI Common Terminology Criteria for Adverse Events v5.0 (CTCAE).
4. Suspected cause of the reaction (i.e. possibly or probably related to one of the following: study intervention, progression of disease, concurrent medications, concurrent illness, or other factors).
5. Patient's response to medical interventions.

9.3 Reporting

Since it is difficult to discern which AEs may impact gait and balance testing, all AEs will be collected, not just neuropathy symptoms. Although unlikely, some unrelated symptoms may impact gait and balance and may also be indirectly related to neuropathy symptoms (e.g. cytopenias and fatigue may impact balance and gait).

10.0 CRITERIA FOR RESPONSE ASSESSMENT

All patients will be considered evaluable. Participants with only baseline measures will be considered as drop-outs.

10.1 Measurement of Effect

We will evaluate effect of EMBr Wave by PRO, primarily HFRDIS. We will also include satisfaction/perceived efficacy questions measuring ratings on a 10-point Likert scale with 10 being most satisfied or most effective.

11.0 DATA REPORTING / REGULATORY REQUIREMENTS

11.1 Ethical and Regulatory Considerations

This trial will be conducted in compliance with the protocol, Good Clinical Practice guidelines, and all applicable regulatory requirements.

11.2 Institutional Review Board

The Principal Investigator will have obtained written approval to conduct the study from The Ohio State University IRB and the Clinical Scientific Review Committee of the James Cancer Hospital and Solove Research Institute. All amendments must be approved by the Institutional Review Board of The Ohio State University prior to implementation.

11.3 Informed Consent

All potential candidates for the study will be given a copy to read of the consent form for the study. The Principal Investigator and/or designee will explain all aspects of the study in lay language and answer all the candidate's questions regarding the study. If the candidate desires to participate in the study, he or she will be asked to sign the Informed Consent. The study agent will not be released to a subject without a signed Informed Consent. Elements of informed consent include explanations of 1) the purpose of the trial, 2) what the study entails, 3) alternate treatments, 4) expenses and inconveniences to be incurred, 5) discomfort and risks to the subject, 6) whether she will receive payment for participation in the study, 7) contact person to call in the event of an emergency, 8) subject rights as a result of illness or injury from trial

participation, 9) subjects right to withdraw from the trial at any time without prejudice, 10) confidentiality of trial participation.

11.4 Patient Confidentiality

The information obtained during the conduct of this study is considered confidential and will not be released without the written permission of the subject, except as necessary for regulatory agencies. Signed consent forms, data sheets, and laboratory notebooks will be kept in locked cabinets in Clinical Trials Office at Stefanie Spielman Breast Center.

11.5 Publication and Research Findings

Publications of the research findings will present data in a format that will not reveal the identity of the participants.

11.6 Compliance Monitoring

In accordance with IRB guidelines, the study program will be reviewed by the IRB every 12 months or less. Deviations from the protocol must be documented in the medical record and reported immediately to the PI. Deviations that meet the criteria for Immediate Event Reporting (http://orrp.osu.edu/irb/event/index.cfm) such as those that increase risks to subjects and/or compromise scientific integrity will be reported immediately to the IRB.

11.7 Data Safety Monitoring

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at their regular Disease Group meetings (at least monthly) and the discussion will be documented in the minutes. The PI of the trial will review toxicities and responses of the trial where applicable at these disease center meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the PI and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with the sponsors, to determine if the trial should be terminated before completion. Serious adverse events and responses will also be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). The PI will also submit a progress report biannually that will be reviewed by the committee per the DSMC plan. All reportable Serious Adverse Events (SAE) will also be reported to the IRB of record as per the policies of the IRB.

11.8 Responsibility for Data Submission

Data are to be submitted via OnCore on a real-time basis, but no less than once every 2 weeks.

11.9 Data and Records

Primary source documents will include forms routinely used at the Stefanie Spielman Comprehensive Breast Center, namely the Breast Patient Information Form, clinic and office notes as well as laboratory and radiology reports, including documentation found in the electronic medical record (EPIC).

11.10 Safety and Monitoring

Adverse events will be monitored by self-reporting of signs and symptoms.

11.12 Documentation

All adverse events must be documented in detail within the medical record. The patient will be observed and monitored carefully until the condition resolves, stabilizes, or its cause is identified. All adverse events, including laboratory abnormalities, will be followed up according to good medical practices. Information to be recorded includes the following:

1. Specific type of reaction.
2. Duration of reaction.
3. Severity/grade of reaction according to the NCI Common Terminology Criteria for
4. Adverse Events 5.0 (CTCAE).
5. Suspected cause of the reaction (i.e. possibly or probably related to one of the following: study treatment, progression of disease, concurrent medications, concurrent illness, or other factors).
6. Changes made in the administration of the study drugs and other actions taken to alleviate the clinical event.
7. Patient's response to medical interventions.

11.13 Reporting

According to FDA regulations (21 CFR 312.32), IND safety reports shall address "any adverse experience associated with the use of a drug that is both serious and unexpected." The IRB will be notified of any adverse event fulfilling the following criteria:

1. The adverse event is SERIOUS (as defined above),
   OR
2. The adverse event is not serious, but is UNEXPECTED and its association with the study drug, device, or research-related procedure is either DEFINITELY, PROBABLY, or POSSIBLY RELATED, or UNKNOWN (as defined above).

Federal policy [45 CFR 46.116(b)(5)] also requires that investigators inform subjects of any important new information that might affect their willingness to continue participating in the research. When an adverse event necessitates changes to the consent/assent form(s) and/or protocol, or that notification is given to currently or previously enrolled subjects, an amendment request will be submitted in conjunction with the adverse event report. The IRB will make a determination whether any new findings, new knowledge, or adverse effects should be communicated to subjects.

In accordance with IRB guidelines, serious adverse events will be reported within 10 days of the investigator's or research staff members' learning of the event to The Ohio State University Institutional Review Board. OSU IRB Event Reports should be submitted through BuckIRB at: http:/orrp.osu.edu/irb/buck-IRB/. Events resulting in temporary or permanent interruption of study activities by the investigator or sponsor to avoid potential harm to subjects should be reported within 48 hours whenever possible.

All events that may represent unanticipated problems involving risks to subjects or others will be promptly reported (as described above), regardless of whether they occur during or after the study, or involve a subject who has withdrawn from or completed study participation. If changes to the research or consent process are proposed as a result of the event or if additional information will be provided to current and/or past participants, an amendment request will also be submitted for IRB review.

Related events involving risk but not meeting the prompt reporting requirements will be

reported to the IRB in summary form at the time of continuing review.

12.0 STATISTICAL CONSIDERATIONS

12.1 Statistical Data Analysis and Study Design

Feasibility will be evaluated primarily with respect to device usage, and secondarily with respect to patient satisfaction. Device usage will be evaluated by the number of minutes and sessions per 24-hour day per participant. The mean patient satisfaction scores for each Likert-type question and proportion of reporting satisfaction scores at or above 7 will be estimated in the entire sample and compared between sequence groups at the 5% significance level (two-sided).

Preliminary efficacy will be evaluated with respect to the Hot Flash-Related Daily Interference Scale (HFRDIS), hot flash number and severity (as a daily hot flash score; DHFS), and patient perception of efficacy (10-point Likert scale items). HFRDIS measurements will be evaluated at the end of each week on the study, and DHFS will be used as recorded in the daily hot flash journal. Repeated measurements will be modeled as repeated outcomes in a linear mixed effects model with fixed effects for treatment, period, and treatment-by-period interaction, and random effects for subjects and for subject-by-treatment interactions to account for correlated measurements within the same subject. The period variable will be represented in the sum-to-zero coding so that the target of inference will be the fixed main effect of treatment, tested at the 5% significance level (two-sided). Thus the treatment effect will be interpreted as time-averaged and estimated using information from the mixed model. Patient perception of efficacy will be evaluated at the end of the device period and estimated in the entire sample and compared between sequence groups.

All analyses will proceed on an intent-to-treat basis. When observations of preliminary efficacy endpoints are missing, the rest of that patient's observations may still be used in the mixed effects model. To assess the potential impact of informative loss to follow-up, we will compare patients who leave the study or cease reporting endpoints to those who provide data for the full study duration. Patients will be compared on the basis of baseline variables and available longitudinal measurements. The pattern of loss to follow-up will be reported via CONSORT chart. Potential impact on estimates will be assessed via multiple imputation. For the purpose of evaluating compliance, patients who leave the study will be recorded as not wearing the device after leaving the study, ensuring that all patients are evaluable.

As an exploratory analysis, individual components of the HFRDIS will be analyzed using the same model as the total HFRDIS. As sensitivity analyses, the preliminary efficacy analyses will be repeated allowing for temporal correlation of measures, and including as covariates any baseline variables with large imbalances.

Our feasibility target is that at least 75% of all patients meet the compliance criteria described above. The minimum number of the 38 enrolled patients meeting the compliance criteria to achieve this threshold is 23 (77%), in which case the 95% Jeffreys interval lower bound is 60% (thus we can rule out population compliance rates below 60%) (Figure 3, left). We expect the population compliance rate to be at least 85%, in which case we have at least 93% probability of

achieving the compliance target (Figure 3, right). With a population compliance rate of 80%, we have a 76% probability of achieving the compliance target.

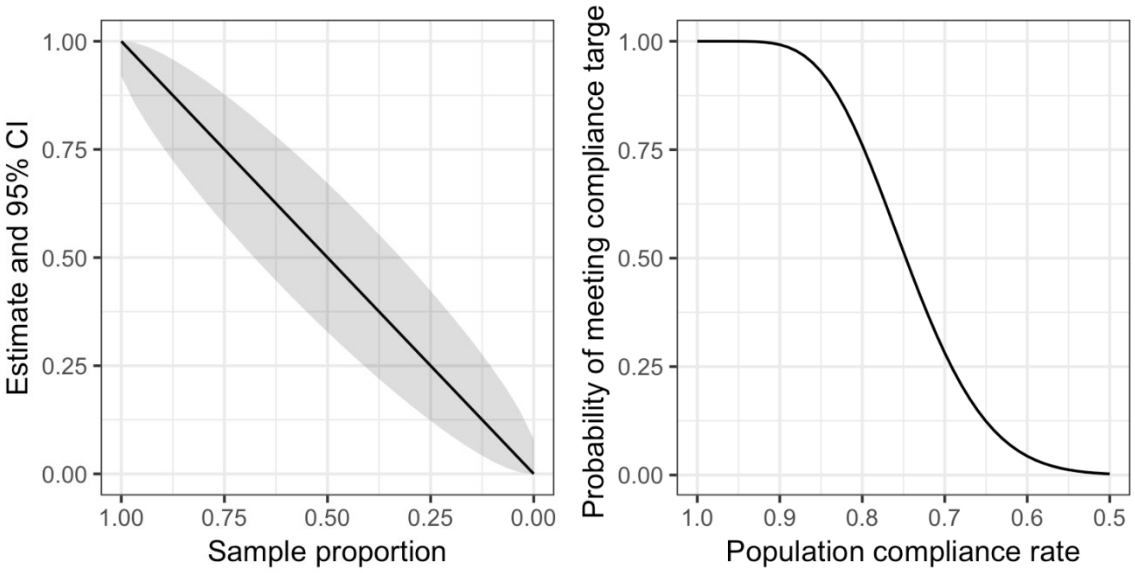

Figure 3: Left: Jeffreys intervals (95% equal tail probability credible intervals from a Beta(0.5, 0.5) prior) corresponding to various sample proportions with 30 patients. **Right:** Probability of achieving target compliance rate for various population rates.

Power to detect a treatment effect with respect to HFRDIS and DHFS measures via the mixed model depend on the size of the average treatment effect relative to the within-subject standard deviation (i.e., Cohen's *d* via the SD of the error term in the mixed model) and the standard deviation of the random within-subject treatment effects. Figure 4 displays study power for different combinations of these factors, estimated via simulation of 1000 datasets per scenario. For instance, if the within-subject SD and individual treatment effect SD are equal, we have 80% power to detect an average treatment effect of 0.7 (Cohen's *d*).

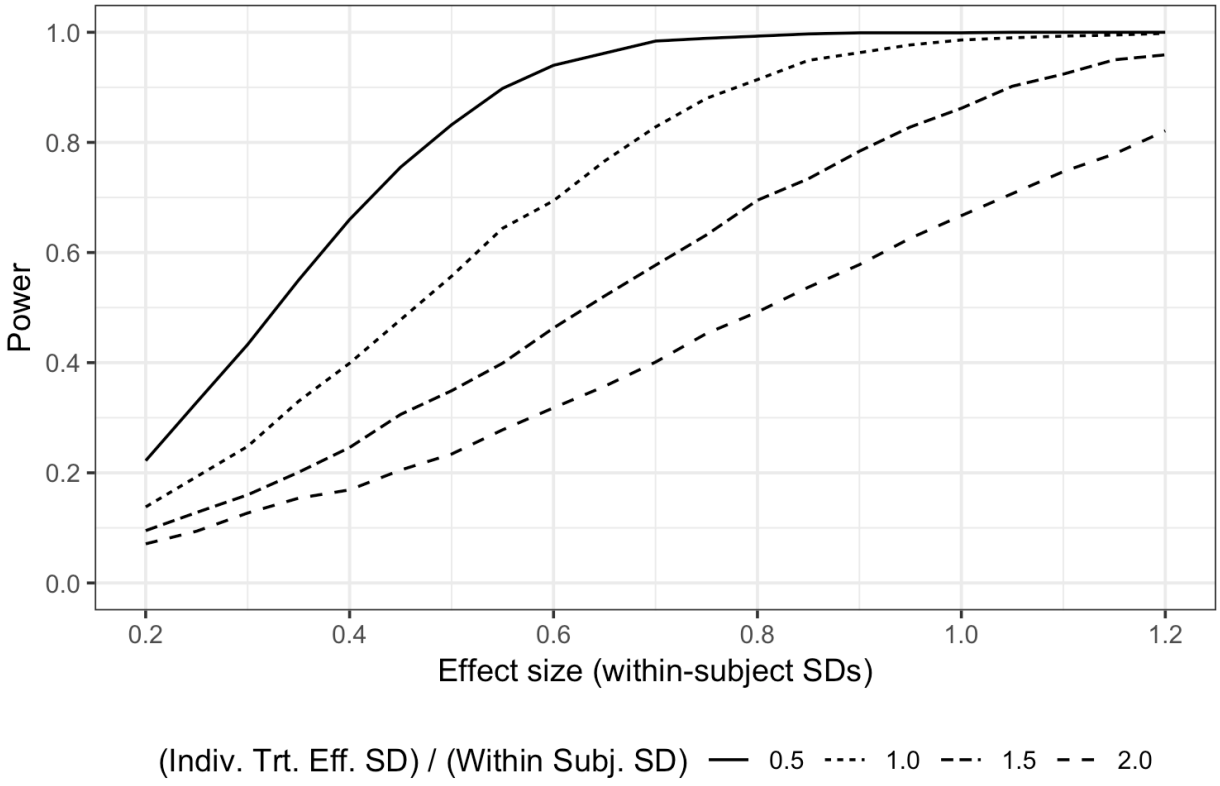

Figure 4: "Indiv. Trt. Eff. SD" is the standard deviation of the individual treatment effects (random slopes in mixed model) and "Within subj. SD" is the within-subject standard deviation during each period (error term in mixed model). Variability of the random intercepts has minimal effect on power.

Data from this study will be used to design future definitive intervention studies to evaluate the efficacy of this intervention in larger randomized studies.

13.0 REFERENCES

1. Gold EB, Colvin A, Avis N, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. *Am J Public Health.* 2006;96(7):1226-1235.
2. Faubion SS, Loprinzi CL, Ruddy KJ. Management of Hormone Deprivation Symptoms After Cancer. *Mayo Clin Proc.* 2016;91(8):1133-1146.
3. Carpenter JS. The Hot Flash Related Daily Interference Scale: a tool for assessing the impact of hot flashes on quality of life following breast cancer. *J Pain Symptom Manage.* 2001;22(6):979-989.
4. Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl H. Methodologic lessons learned from hot flash studies. *J Clin Oncol.* 2001;19(23):4280-4290.