Double Blind Randomized Controlled Crossover Pilot Evaluation of Wrist Cooling Devices on the Severity of Hot Flashes for Women and Men Who Suffer from Moderate and or Severe Hot Flashes

Protocol Version Number: 1.8
Protocol Version Date: 01/23/2024
ClinicalTrials.gov number: NCT05595213
H-43277
Funding Mechanism: Internally funded. Devices supplied by manufacturer.

Principal Investigator: Michael F. Holick
Phone: 617-358-6139
E-mail: mfholick@bu.edu

Statistical Analysis Plan -page 22

CONFIDENTIAL

Summary of Changes:
The table should summarize changes of IRB-approved versions of the protocol, including a description of the change and rationale.

Version	Date	Description of Change	Brief Rationale
1.8	1/23/2024	To expand recruitment by advertising on social media.	We will be able to expand the pool of subjects thereby have to ability to complete the recruitment more efficiently.
1.6	10/24/2023	To expand recruitment by enrolling subjects who meet the inclusion criteria locally or virtually.	We will be able to expand the pool of subjects thereby have to ability to complete the recruitment more efficiently.
1.5	8/1/2023	Revised protocol and consent form to be the same as the approved consent form regarding blinding.	Responding to IRB stipulation.
1.4	06/05/2023	To expand recruitments by including all women and men who meet the	We now will be able to include subjects with the most common

		inclusion criteria of having at least 2 moderate or severe hot flashes daily for the past 2 months. There will no longer be a requirement for the women and men to be on hormone deprivation therapy.	causes of hot flashes i.e., post-menopausal women and women who have surgically induced menopause.

TABLE OF CONTENTS

1 List of Abbreviations

None

2 Protocol Summary

Title:	Double Blind Randomized Controlled Crossover Pilot Evaluation of Wrist Cooling Devices on the Severity of Hot Flashes for Women and Men Who Suffer from Moderate and or Severe Hot Flashes
Population:	Thirty adult women and men experiencing at least 2 hot flashes a day for at least the past 2 months that are either moderate and/or severe in intensity.
Intervention:	Wrist cooling devices placed on the wrist.
Objectives:	To determine the effect of two wrist cooling devices on symptom control of hot flashes in adult women and men experiencing at least 2 hot flashes daily for at least the past 2 months that are of moderate and/or severe in intensity.
Design/Methodology:	This pilot randomized double blind controlled crossover study aims to determine the impact of two wrist cooling devices on symptom control of hot flashes in adult women and men experiencing hot flashes. We will recruit 30 adults experiencing bothersome moderate and/or severe hot flashes at least twice a day for at least the past 2 months. We plan to conduct the study at BUSM, locally or virtually. **<u>Subjects who will be seen at BUSM or locally;</u>** 1. If the potential subject passes the pre-screen and agrees to participate, he/she will be invited to participate in the clinical trial. The subjects who meet the inclusion criteria to participate in the study and who wish to be consented by the PI will meet with the subject in person and follow the consenting procedure as outlined in the protocol. The subjects who were given the consent form will have an opportunity to read it and ask questions of the PI or study personnel. The potential subjects will be given up to 30 minutes to decide if they want to participate. The PI will then ask them to sign the consent form. Once the signed consent form is obtained, it will be signed by the PI who reviewed the consent form with the subject and put into their

file. After the PI signed the consent form, the consent form will be copied, and the copy will be given to the subject.

2. The subjects who are seen and after completing consenting process will receive the two devices and diaries and will be contacted as outlined in the approved protocol.
3. The subjects will return the devices and diaries to the PI or study personnel as outlined in the protocol. They will also have the option to receive the commercially available device after completion the study as outlined in the protocol.

Subjects who will be seen virtually:

1. If the potential subject passes the pre-screen and agrees to participate, he/she will be invited to participate in the clinical trial. The subject who meets the inclusion criteria to participate in the study and who wish to be consented virtually the PI will meet with the subject by zoom to follow the consenting procedure as outlined in the protocol. The subject will be provided the consent form by email. The subject will have an opportunity to read it and ask questions of the PI or study personnel. The potential subject will be given up to 30 minutes to decide if they want to participate. The PI will obtain a verbal consent by asking the subject do they agree with the consent form? If they agree, the PI or study personnel will document the subject's consent agreement, and this will be noted in the subject's study file. The date and time will be recorded. You will receive the signed consent form documenting your verbal acceptance by email.
2. After obtaining verbal consent, the subject will be randomized as outlined in the approved protocol. The subjects who were consented by zoom and who had provided their verbal consent to the PI or study personal will then receive the devices and diaries by United Parcel Service (UPS), United States Parcel Service (USPS) or by Federal Express (FEDEX) that will have a tracking number and signature request documenting that subject received the devices and diaries.
3. The subject who will be participating virtually will be required to return the devices and diaries to the PI or study personnel by

using the UPS, USPS, FEDEX return box that will have a return address, tracking number and signature request documenting that subject received the devices and diaries. The return box will have an account number to pay for the return of the devices and diaries. Once the devices and diaries have been received by either the PI or study personnel, the subject will have the option to be sent the commercially available device.

The participants will be randomly assigned to wear one of the two wrist cooling devices that have an identical appearance during weeks 3 and 4 of the study and then use the other device during weeks 5 and 6 of the study. The devices will be attached to the wrist with the white plate placed on the interior side of the wrist. When activated, one device will turn on a cooling fan with the white plate being active and cooling the skin for up to 5 minutes, and the other device will turn on a cooling fan only for up to 5 minutes without the white plate being active to cool the skin. We will try to recruit 50% men and 50% women.

We will use a 3-category diary for hot flash symptom monitoring (assessed as mild, moderate, and severe). This study will take at least 6 weeks and up to 8 weeks requiring the participants to see a study team member either in person or virtually at the beginning and end of the study. The participants will receive three phone calls/ zoom calls during the study to remind them of when to use each device. The participant will be instructed that for the first 2 weeks that he /she will document as soon as possible in the Hot Flash Diary his/her daily each experience with hot flash and record the severity of each hot flash in the diary without using any device. They will then be instructed at the beginning of week 3 to use the device that they were randomly assigned to use. They can wear the device 24/7, i.e., all the time or they can place it on their wrist when they begin to experience a hot flash. They will be asked to fill in their Hot Flash and Device Use Diary as soon as possible after the hot flash the severity of each of their hot flashes that they experienced throughout the day and night. They will also be instructed at the time that they are documenting in the diary the severity of the hot flash as to whether or not they used the device while having the hot flash in the same

	diary. They will continue this activity for 2 weeks and then be instructed to use the second randomly assigned device at the beginning of week 5. They will use this device during weeks 5 and 6 of the study documenting as soon as possible in their diary the severity of each hot flash and whether or not they used the device during the hot flash. They will be instructed after the 6 weeks to have either an in person return visit or a virtual return visit. Those subjects who are participating at BUSM or locally will be given the diaries and the devices to the study personnel. Those subjects who are participating in the study virtually will be asked to return the diaries and devices by FEDEX, UPS or USPS. During the last visit subjects who are participating in the study at BUSM or locally will have the option to receive the commercially available wrist cooling device as compensation. Those subjects who are participating in the study virtually will have the option to be sent the commercially available wrist cooling device as compensation by FEDEX, UPS or USPS.
Total Study Duration:	**1 year**
Subject Participation Duration:	At least 6 weeks and up to 8 weeks

3 Background/Rationale & Purpose

3.1 Background Information

A hot flash is a sudden, temporary onset of body warmth, flushing, and sweating (often associated with menopause). This symptom is associated with women and men who suffer from moderate and or severe hot flashes.

3.2 Rationale and Purpose

There have been numerous studies with nonhormonal pharmaceutical interventions including antidepressants, gabapentin and black cohosh with minimum demonstrable benefit to reduce severity and duration of hot flashes. Other techniques including electrical stimulation with acupuncture provided some short-term relief (1-3).

Temperature management therapy has been proposed to be an alternative method to control hot flashes. However, there has been no previous data on the efficacy of a wrist cooling device on hot flash symptom control. We aim to conduct a pilot double-blind randomized crossover study to evaluate the

effectiveness of 2 wrist cooling devices on the severity of hot flashes. This study will be conducted in women and men who experience at least 2 hot flashes daily for the past 2 months that are either moderate or severe in intensity.

4 Objectives

4.1 Study Objective

To determine the effect of using a wrist cooling device with an active cooling fan and active cooling porcelain plate versus a wrist cooling device with an active cooling fan and an inactive cooling porcelain plate on the severity of hot flashes occurring in adult women and men who experience daily at least 2 moderate and/or severe hot flashes for at least the past 2 months.

4.2 Study Outcome Measures

4.2.1 Primary Outcome Measures

Daily severity (mild, moderate, and severe) of hot flashes that the participant records in their diary.

4.2.2 Secondary Outcome Measures

Daily use of whether they did or did not use the wrist cooling device during their hot flash that will be recorded in their diary during the last 4 weeks of the study.

4.2.3 Exploratory Outcome Measures

There is no exploratory outcome in this study.

5 Study Design

This pilot randomized double blind crossover study aims to determine the impact of two wrist cooling devices on symptom control of hot flashes in adult women and men experiencing moderate and/or severe hot flashes for at least the past 2 months.

6 Potential Risks and Benefits

6.1 Risks

The most common risks of the wrist cooling device in this study include a reaction that impairs blood flow to the hand and could make it worse for disorders such as Raynaud's phenomenal which is why people with Raynaud's and similar conditions should not take the part in the study. The participant may also experience the coolness as being uncomfortable.

To minimize the risk of adverse events, we will exclude subjects with any history of cold sensitivity to the wrist or hand. In addition, the participant may find the attachment of the device around the wrist to be uncomfortable. We will exclude subjects with a history of experiencing discomfort when placing anything such as a wristwatch on their wrist.

To mitigate discomfort for the device that when activated results in white plate cooling the skin underneath it to a temperature of 47°F we will instruct the participant to press the square button and the temperature will almost immediately increase to 60°F. If it is still uncomfortable the participant has the option of pressing the button again to further increase the temperature to 77°F. They have the other option to shut it off by holding the button down for 2 seconds. The device can also be removed immediately from the wrist which is attached by a Velcro connection that can be easily opened. To mitigate any discomfort for the device that when activated turns on the cooling fan only they will be instructed to press the square button for 2 seconds which will set off the device or they can immediately remove the device from their wrist.

6.2 Potential Benefits

There may be a direct benefit to the participant by the device reducing the severity of their hot flashes. However, the likelihood and degree of the benefit is currently unknown given lack of prior clinical data to support the use of this device.

6.3 Analysis of Risks in Relation to Benefits

The risk associated with the device is discomfort and Raynaud phenomenon, which will be minimized by excluding participants with a history of these conditions. We expect that the possible benefit from the device in reducing the severity of hot flashes that the participant experienced.

7 Study Subject Selection

7.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

a. Experiencing at least 2 hot flashes per day that are either moderate and/or severe in intensity for at least the past 2 months.

- Moderate hot flash: sensation of heat with sweating/dampness but able to continue activity with only brief fanning needed
- Severe hot flash: sensation of intense heat with sweating and causing disruption of current activity

b. English speaking and English writing ability

c. Must be 21 years old age or older

7.2 Subject Exclusion Criteria:

An adult who meets any of the following criteria will be excluded from participation in this study:

1. Temperature sensitivity due to cooling associated with an autoimmune or vascular disorder, such as Raynaud's phenomena, peripheral arterial disease or for any other reasons.
2. Any wrist skin sensitivity that is known to cause discomfort when any type of device such as a wristwatch is placed on the wrist.
3. Any lack of sensitivity to coolness on the wrists or hands
4. Current use of pharmaceuticals or devices to treat hot flashes.
5. Unable to understand and speak English and unable to write English

8 Study Intervention:

The subject will be randomized using the computer-generated randomization chart that will be produced by Dr. Charoenngam. Dr. Charoenngam will not be involved in any of the studies activities associated with interacting with this subject. The subject will be randomized in this double blinded randomized crossover study to use assigned device the depending upon their randomization during weeks 3 and 4 followed by using the other assigned device during weeks 5 and 6. For example, if the subject was randomized to use the device in box B for weeks 3 and 4 then they will be instructed to use the assigned device that in the box A for weeks 5 and 6 of the study. The wrist cooling device. The randomization chart will be given to Dr. Alexandrian whose only activity is to keep the chart until the study is unblinded.

<u>Wrist cooling device with a cooling porcelain plate</u>

- The name of the device is Kulkuf
- Device size is 11.25 inches long and is 2.5 inches in width
- Device model is Kulkuf wrist cooling device. One of the devices when turned on will have the fan and wrist cooling porcelain plate activated while the other device that is identical in appearance will have the fan working when turned on and the cooling porcelain plate inactivated.

- The device contains a mini heat pump attached to a Velcro open sleeve that can be wrapped around and attached to the wrist (Figure 1).
- The device that when turned on results in the cooling fan and cooling porcelain plate to be activated has 3 settings when the square bottom is depressed. When first depressed the device is immediately turned on and generates a cool temperature of 47°F. When the square bottom is depressed a second time the temperature increases to 60°F. When the square button is pressed a third time the temperature increases 77°F. When the square bottom is held down for two seconds the device will stop operating. The device automatically shuts off after 5 minutes.
- The device that when turned on results in the cooling fan being turned on will have the heat pump deactivated and therefore the white cooling porcelain plate will not cool the skin.
- The device will be used whenever a hot flash occurs during weeks 3, 4, 5 and 6 of the study.
- Dhama USA is the manufacturer of the device.
- The devices will be stored in the locked cabinet in Dr. Holick's office.
- *The devices will be supplied at no cost to the subject.*

Wrist cooling device. On the left panel of figure 1 is the front and back of the device that has the cooling porcelain plate (white square). The device is wrapped around the wrist with the cooling porcelain plate on the inside of the wrist (figure 1 right panel). The device will be provided to the subject with the removal of the A or B label (Figure 2). The cooling devices in both boxes are identical in appearance. The subject will place the device on their wrist using the Velcro attachment. Briefly, when activated by pushing the square button the cooling fan in both devices is activated. One of the devices when activated will also have the cooling porcelain plate almost immediately begin to cool to a temperature of 47°F while the other control device will not activate the cooling porcelain plate. If the cooling temperature is uncomfortable the participant will have an opportunity to press the button again and the temperature will increase to 60°F. If this remains uncomfortable the participant can press the button a third time and the temperature will rise to 77°F. For the device that has the fan turned on only the participant can press the square button for 2 seconds to turn it off if for some reason it becomes uncomfortable. The alternative for both devices if uncomfortable the device can be easily removed from the wrist.
The devices will be supplied by the company at no cost and will be stored in Dr. Holick's laboratory.

Figure 1: Wrist cooling device. On the left is the front of the device and on the right is the back of the device that has the cooling porcelain plate. The device is wrapped around the wrist with the cooling porcelain plate on the inside of the wrist.

Figure 2: Boxes labeled A and B will be randomized and after the randomization the A and B labels will be removed on the front of the box. The following language "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use" to comply with the abbreviated IDE requirements under §812.5 for labeling a nonsignificant risk device.

9 Recruitment and Retention Procedures:

9.1.1 Recruitment Procedures

Physicians including oncologists, urologists, endocrinologists, gynecologists, general medicine practitioners, physician assistants, nurse practitioners and other health care professionals at Boston University Medical Campus who see patients who complain of hot flashes, will be contacted by phone or email informing them of the study. For those physicians and health care professionals who are interested in having their patients be aware of this study we will provide copies of a BU Communications/IRB approved flyer explaining the study. They will be provided with a flyer as a hard copy either as a 8x10 flyer or 4x4 flyer that can be placed in their pocket for easy distribution. Alternatively, they will be provided a PDF of the BU communications/IRB approved flyer. The doctor or healthcare professional will have the

option to provide to Dr. Holick prospective patients who meet the exclusion and inclusion criteria their contact phone number or instruct the patient to call him directly. The patient may call Dr Holick as a result of seeing the flyer. We will advertise for this study at the Boston University Medical campus via study flyer, on the BU communications sites and on social media. We would like to expand our recruitment capability by including subjects who have contacted Dr. Holick about their interest in participating in the study as a result of seeing the study posted on the ClinicalTrials.gov or hearing about the study from a physician, family member or friend. These interested subjects will be recruited virtually by zoom or meet Dr. Holick or a study personnel locally outside of the Boston University Medical Campus. Only after they meet all of the requirements in the protocol including the inclusion and exclusion criteria will they be enrolled in the study either locally or virtually.

9.1.2 Retention Procedures

The subject will be contacted by study personnel via telephone or zoom call 1-3 days before the expected date he/she will use the device during weeks 3 and 4 of the study and then a telephone or zoom call 1-3 days before the expected date when the participant will use the other randomly assigned device during weeks 5 and 6. The subject will be contacted during week 6 of the study before the study end date to remind them to come back and return the diaries and devices at their scheduled visit that was provided to them during their first visit. Those subjects who are participating in the study virtually will be contacted during week 6 of the study before the study end date to remind them to return the diaries and devices by FEDEX, UPS or USPS.

10 Screening Procedures

Once subjects have responded to the study flyer, ClinicalTrial.gov or word of mouth, they will be screened over the phone or by zoom to determine eligibility using brief screening agreement and pre-screening questionnaire. During the preliminary screening call, the subject will be asked about their medical history and inclusion/exclusion criteria. Completion of the preliminary anonymous screening for the potentially eligible participants will be documented in the study binder. The information to be retained in the study binder include study ID and answers to the pre-screening questionnaire. For the individuals with screening failure, no information will be retained. Once the subjects are determined to be eligible, they will be scheduled for their first visit to our clinical research space in the Vitamin D, Skin, and Bone Research Laboratory, located at 85 E Newton St, M-1013 Boston, MA 02118 (BUSM), locally or virtually. The PI will consent the subjects either in person or virtually by zoom.

The eligibility data will be stored in Dr. Holick’s offices under lock and key. The door to Dr.Holick's lab is accessed by those who have ID access to the lab. Electronic information will be stored on a departmental

server ("Y"drive) which is password protected. Paper records will be stored in a locked room for which only study staff will have access to. Master list will be stored on the Y-drive and will not be stored with study data. All other electronic data will be on the Y-drive which is password protected. Paper master list will be stored and locked in M1013; only study staff and study coordinator have access to this room. For individuals with screening failure, data including answers to the screening question, contact information and identifiable information will not be retained and will be destroyed on the day of the pre-screening process.

11 Consent Procedures

All interested potential subjects, will undergo a prescreening questionnaire to determine eligibility. If the potential subjects passes the pre-screen, he/she will be invited to participate in the clinical trial.

Subjects who will be seen at BUSM or locally;

- If the potential subject passes the pre-screen and agrees to participate, he/she will be invited to participate in the clinical trial. The subjects who meet the inclusion criteria to participate in the study and who wish to be consented locally the PI will meet with the subject in person and follow the consenting procedure as outlined in the protocol. The subjects who were given the consent form in-person will have an opportunity to read it and ask questions of the PI or study personnel. The potential subjects will be given up to 30 minutes to decide if they want to participate. The PI will then ask them to sign the consent form. The subject who signs the consent form in person and will give the signed consent form to the PI or study personal. Once the signed consent form is obtained, it will be signed by the PI who reviewed the consent form with the subject and put into their file. After the PI signed the consent form, the consent form will be copied, and the copy will be given to the subject.
- The subjects who are seen and after completing consenting process will receive the two devices and diaries and will be contacted as outlined in the approved protocol.
- The subjects will return the devices and diaries to the PI or study personnel as outlined in the protocol. They will have an option to receive the commercially available device after completion the study as outlined in the protocol.

Subjects who will be seen virtually:

- If the potential subject passes the pre-screen and agrees to participate, he/she will be invited to participate in the clinical trial. The subject who meets the inclusion criteria to participate in the study and who wish to be consented virtually the PI will meet with the subject by zoom to follow the consenting procedure as outlined in the protocol. The subject will be provided the consent form by email. The subject will have an opportunity to read it and ask questions of the PI or study personnel. The potential subject will be given up to 30 minutes to decide if they want to participate. The PI will

obtain a verbal consent by asking the subject do they agree with the consent form? If they agree, the PI or study personnel will document the subject's consent agreement, and this will be noted in the subject's study file. The date and time will be recorded.

- After obtaining verbal consent, the subject will be randomized as outlined in the approved protocol. The subjects who were consented by zoom and who had provided their verbal consent to the PI or study personal will then receive the devices and diaries by United Parcel Service (UPS), United States Parcel Service (USPS) or by Federal Express (FEDEX) that will have a tracking number and signature request documenting that subject received the devices and diaries.
- The subject will be required to return the devices and diaries to the PI or study personnel by using the UPS, USPS, FEDEX return box that will be given to them. The return box will have an account number to pay for the return of the devices and diaries. The box will also contain a return address and have a tracking number. Once the devices and diaries have been received by either the PI or study personnel, the subject will have the option to be sent the commercially available device.

12 Study Procedures

See the Appendix for the schedule of events.

During the screening process, potential participants will be asked with prescreening questionnaire to determine eligibility. Once they are determined to be eligible, they will be invited to participate in the study.

This study will take at least 6 weeks and up to 8 weeks. In the first visit in person or virtually this is expected to last up to 1 hour, the participant will be given a consent form and have an opportunity to read it. The study personnel or PI will review the information on the consent form and conduct consent discussion. The subject will have an opportunity to ask questions of the PI or study personnel before signing it in person or providing verbal consent virtually. After signing the consent form or giving verbal consent, it will be signed by the PI or study personnel and printed out and put into their file. A copy of the fully signed consent form for subjects who have been seen personally by the PI or study personal will be provided a copy of the signed consent form either in person or by email. The subjects who were consented verbally will receive by email the consent form signed by PI or study personnel with documentation of the time and date that the verbal consent was obtained. Once consenting is complete, the subjects who are seen in person will be given the diaries and the two devices. Those subjects who have completed the consenting process will receive the diaries and two devices by FEDEX, UPS or USPS. The participant will be shown how to attach the devices to their wrist and then shown how to activate the devices and control the temperature and to shut it off either in person or virtually. Written instructions will also be provided to the participant for their reference (see the attachment).

The participant will be instructed that for the first 2 weeks that he/she will document in the diary labeled as Hot Flash diary each hot flash rating it as severe, moderate, or minimal without using the device. Study personnel will contact the participant by phone or zoom call 1-3 days before the expected date to start using the device that they were randomly assigned to use. During this call, they will be instructed at the beginning of week 3 to open up one of the two boxes (depending on which arm they are randomized into) that they were given during the first visit and begin using it. The device will be in the box with labeled instructions. They will be instructed that they can wear the device 24/7 i.e. all the time or they can place it on their wrist when they begin to experiencing a hot flash. The study personnel will also explain that during weeks 3 and 4 they will now be using the diary labeled as Hot Flash and Device Use. The study personnel will go over how to use this diary and how to record the severity of their hot flash and document whether or not they used the device.

If you are not available to use the device at the beginning of week 3, you will be allowed to keep documenting the severity of the hot flashes without using the device for another 2 weeks +3 days. You will be contacted by phone or zoom call again 1 – 3 days prior to the date you expect to start using the device.

At the end of week 4, they will be contacted again by the study personnel to stop using the current device and change to the second one that they were randomly assigned to use. They will continue to use the device and document the same information during weeks 5 and 6 of the study. Subjects who were seen in person will be instructed to return and see the PI or one of the study personnel after completing the activity and give the diaries and the devices to the PI or study personnel. Those subjects who are participating in the study virtually will be instructed to return and see the PI or one of the study personnel by zoom after completing the activity and return the diaries and the devices to the PI or study personnel by FEDEX, UPS or USPS. They will be asked questions about the use of the devices. During this in person or virtual visit, all participants will have the option to receive the commercially available wrist cooling device (valued at $199), as compensation either in person or by FEDEX, UPS or USPS.

In summary, there will be a total of two in-person visits for BUSM and local subjects and no in person visit for those are participating virtually 1.) During the first visit the subject will undergo consent process and randomization. Those subjects participating at BUSM or locally will receive the two devices and the diaries. Those subjects participating virtually will receive the two devices and diaries by FEDEX, UPS or USPS. They will be instructed how to use the diaries and the devices at the appropriate time. 2.) During the return visit at the end of the study the subject will be asked questions about the use of devices, and they will return the diaries and the devices either in person or by FEDEX, UPS or USPS. They will have the option to receive the commercially available cooling device as compensation for their participation in this study. There will be 3 telephone or zoom call visits including 1-3 days before the subject is scheduled/expected to use the assigned device during weeks 3 and 4 of the study and then a Zoom call our phone call 1-3 days before the subject is scheduled/expected to use the other device during weeks 5

and 6 of the study. There may be multiple follow-ups calls if the subject is unable to start using the device on the indicated day. During week 6 before the end of the study they will get a reminder call to come back to return the diaries and the devices. The subjects in the virtual study will be reminded to send back the diaries and devices.

This is a double blinded crossover study; the devices will be in boxes that will be labeled as A or B. Only one co-investigator (Dr. Alexanian), who will not be communicating with the subjects will possess the information as to which one (A or B) of the labeled boxes that have a wrist cooling device that when turned on activates the fan and cooling porcelain plate or a wrist cooling device that when turned on only activates the fan. We will unblind the labels at the completion of the study for data analysis.

13 Assessment of Safety and Data Safety Monitoring Plan (DSMP)

13.1 Definitions for Safety Assessment

The following definitions will be used in the assessment of safety:

Adverse Event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Serious Adverse Event (SAE) is any adverse event that

(1) results in death;
(2) is life-threatening;
(3) results in inpatient hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;
(5) results in a congenital anomaly/birth defect; or
(6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Life-threatening means that the event places the subject at immediate risk of death from the event as it occurred.

Unanticipated Problem is defined as an event, experience or outcome that meets **all three** of the following criteria:

- is unexpected; AND
- is related or possibly related to participation in the research; AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

13.2 Safety Review

Both the risks listed in Section 4.1 and unknown risks will be monitored as follows: the participants will be given written and verbal instruction during the consenting process and at each telephone/zoom call will be asked if they have experienced any adverse effects. The subject will also have the opportunity to contact the study personnel or PI if they experience any adverse effects or significant discomfort from coolness among others.

13.2.1 Multi-Site Safety Monitoring

This is not a multi-site study.

13.3 Reporting Plans

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems, safety monitors' reports, and Adverse Events to the BMC/BU Medical Center IRB in accordance with IRB policies:

- Unanticipated Problems will be reported to the BMC/BU Medical Campus IRB within 7 days of the investigator learning of the event.
- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.

13.4 Stopping Rules

The study has no pre-defined stopping rules since that devices are considered to be nonsignificant risk devices.

14 Data Handling and Record Keeping

14.1 Confidentiality

Subjects are assigned a code after consent and enrolled in the study. All coded records containing subject information will be stored in Dr. Holick's offices under lock and key. Data will be kept in the Dr. Holick lab (M-1011). The door to the Vitamin D lab is accessed by those who have ID access to the lab. The data will be coded and after 7 years will be deidentified and kept indefinitely. Electronic information will be stored on a departmental server ("Y"drive), which is password protected. Paper records will be stored in a locked room for which only study staff will have access to. Master list will be stored on the Y drive and will not be stored with study data. All other electronic data will also be stored on the Y-drive which is password protected. Paper master list will be stored and locked in M1013; only study staff and study coordinator have access to this room. All locations where data will be kept are inaccessible to the public. Data will be available only to study personnel. Data will be kept in a locked room. Study code will be used for all study data that is collected. The study coordinator and study staff will keep the subject list on a secure network drive, which is password accessible only.

To maintain confidentiality for the zoom calls the zoom call will only be made at Boston University School of Medicine that is password protected or by zoom on a laptop computer that is connected to the VPN of Boston University School of Medicine.

14.2 Study Documentation, Source Data

Data generated by the methods described in the protocol will be recorded. Data may be transcribed legibly for each subject or directly inputted into an electronic system or any combination thereof.

14.3 Study Records Retention

Study records will be retained for at least seven years after completion of the study. Documentation of informed consent of subjects will be retained for at least seven years after the study is closed, unless the IRB waived the requirement for informed consent or documentation of informed consent. Such records may be preserved in hardcopy, electronic or other media forms and must be accessible for inspection and copying by authorized individuals.

15 Statistical Plan

15.1 Study Hypotheses

We hypothesize that the wrist cooling device with a cooling porcelain plate more effective than the wrist cooling device with a fan only in reducing the severity of the hot flash.

15.2 Sample Size Determination

Reviewing the different types of treatment for hot flashes showed that the mean number of hot flashes per week decreased by 30%, 58%, 71% and 85% by Yoga poses, Citalopram, pregabalin and Gabapentin respectively. Also, hot flashes were reduced by 15-20% in the group receiving placebo.

We want to consider the sample size of a balanced, cross-over design and the within mean square error from the ANOVA table will be used to analyze crossover design.

We need 11 participants in each group to detect a 40% difference (average 60% reduction in severity in the treatment group and 20% reduction in severity in the placebo group) with 80% power using two-sided significance level of 0.05.

Therefore, with the expected 25% drop-out rate, we will recruit a total of 30 participants (15 per arm).

15.3 Statistical Methods

The ANOVA table for crossover design will be used for statistical analysis.

16 Ethics/Protection of Human Subjects

This study is to be conducted according to applicable US federal regulations and institutional policies (which are based in federal regulations, guidance, and ICH Good Clinical Practice guidelines).

This protocol and any amendments will be submitted to the Boston Medical Center and Boston University Medical Campus IRB for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB. The consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. Consent will be documented as required by the IRB.

We will conduct a blinding index evaluation at the end of the study. This will be accomplished by standardized questionnaire that will be used to ask the subject about the use of the devices. The participants will be asked if they believe that they were assigned to the (i) control or (ii) treatment groups, or (iii) if they are uncertain of their assignment (the “don’t know” response).

We will use a minor modified questionnaire published by
Williams SL, Ferrigno L, Maraini G, Rosmini F, Sperduto RD. A post-trial survey to assess the impact of dissemination of results and unmasking on participants in a 13-year randomised controlled trial on age-related cataract. Trials. 2011 Jun 14; 12:148. doi: 10.1186/1745-6215-12-148. PMID: 21672204; PMCID: PMC3136405.

17 Literature References

1. Schrock NM et. al. pilot study to determine the effects of dronabinol on hot flash relief in breast cancer patients. Journal of Clinical Oncology, 22 (14): 8189, 2004.

2. Mao JJ et al. Electro Acupuncture versus gabapentin for hot flashes among breast cancer survivors: A randomized placebo-controlled trial. Journal of Clinical Oncology. 33 (31): 3615-3620; 2015

3. De Boer H. et al. Luteinizing hormone-releasing hormone and postmenopausal flushing. New England Journal of Medicine. 361: 1218-1219, 2009.

4. Guttuso T. Review of hot flashes diaries. Maturitas 71: 213-216; 2012

18 Appendix

Schedule of Events

	Baseline	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**
	In-Person/ Virtually	**At home**						**In-Person/ Virtually**
Consent + HIPAA Authorization	X							
Eligibility Confirmation	X							
Receive Hot Flash Diaries and receive instruction how to use them	X							
Receive Two Devices and receive instruction how to use them	X							
Use of Hot Flash Diary		X	X					
Use of Hot Flash and Device A Diary				X	X			
Use of Hot Flash and Device B Diary						X	X	
Telephone/zoom call			X		X		X	

Intervention – Wear the first device				X	X			
Intervention – Wear the second device						X	X	
You will either return to see Dr. Holick or one of his assistants to return the devices and the diaries or send the devices and diaries to Dr. Holick or one of his assistants by FEDEX, UPS, USPS. *You will then have the option to receive the commercially available wrist cooling device. You will also be asked questions about the use of the devices.*								X

Note: The subject will be allowed to monitor hot flash symptom without using the device for up to 4 weeks +3 days.