University of Colorado
Colorado Springs (UCCS)
Consent to be a Research Subject

Title: Hot water therapy for the treatment of menopause-related hot flashes and other symptoms: a clinical trial

Principal Investigator: Nathan Morris

Funding Source: University of Colorado at Colorado Springs

Key Information
Your consent to participate in this study is being requested and participation is voluntary. If you choose to give your consent to participate in this study, you are free to withdraw from the study at any time. The purpose of this research is to determine whether hot water therapy (i.e. taking prolonged hot baths on multiple consecutive days) decreases hot flash symptoms and improves mood in women who are undergoing or who have underwent menopause. It is reasonable to expect that you will feel hot and may sweat while bathing and during your physiological assessment tests. It is also reasonable to expect that you may experience some discomfort from the insertion of the rectal and esophageal probes used to measure core temperature. You may benefit from participating in this study as we believe that hot water therapy will reduce menopause-related symptoms, especially hot flashes, but this is not guaranteed. You will also be compensated with a $100 gift certificate if you complete all requirements outlined for this study.

Introduction
You are being asked to be in a research study. This form is designed to tell you everything you need to think about before you decide to consent (agree) to be in the study or not to be in the study. A member of the research team will describe this study to you and answer any questions. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.**

Before making your decision:
- Please carefully read this form or have it read to you.
- Please ask questions about anything that is not clear.

Feel free to take your time thinking about whether you would like to participate. By signing this form, you will not give up any legal rights.

Study Overview This study plans to test whether hot water bathing can improve symptoms common with menopause, especially hot flashes. We expect that hot water therapy will reduce the intensity of these symptoms, particularly for those who experience hot flashes. If hot water therapy is found to be an effective and feasible intervention, it would provide women going through menopause an alternative or additive treatment to hormone replacement therapy.

This trial will be registered and may report results on www.ClinicalTrials.gov or some other Federally sponsored site that is publicly available.

Procedures You are being asked to be in this research study because you are a healthy woman who has either gone through, or is going through, menopause and is experiencing hot flashes and potentially other symptoms of menopause (e.g. night sweats, mood disturbances, etc.), are not currently on or plan to start hormone replacement therapy in the near-future and have not been diagnosed with any cardiovascular diseases. If you agree to be a research participant, you will be scheduled for up to 13 lab visits in either rooms 311, 313, or 334 (the climate chamber) in the Hybl Sports Medicine and Performance Center on the UCCS campus. Each of the three physiological assessment visits will take ~3

hours to complete and each hot water therapy session will take ~2 hours to complete (~29 hour total time commitment). All visits are voluntary and you may choose to discontinue your participation in the study at any time.

Preliminary visit: During a preliminary visit to the lab, we will walk you through all the procedures to be used in the study and will answer any questions you may have before you consent to participate.

Initial tracking period: For at least two weeks before the study, we will ask you to record the intensity and frequency of your hot flashes daily and other menopause related symptoms weekly with questionnaires that will be provided to you during the preliminary visit.

Physiological assessments: On days 1, 7, and 13 of your heat therapy sessions, we will ask you to come to a climate chamber (room 334) at the Hybl center to have your thermoregulatory responses assessed. This will consist of slowly walking on a motorized treadmill in 99.5°F (37.5°C) and 30% relative humidity conditions, for 30 min after which the humidity in the climate chamber will be progressively increased until your core temperature begins to increase (~2 hour total time). Before and/or during these trials, core temperature, heart rate, whole-body sweat losses, thermal comfort, local sweat rate, and skin blood flow will be measured, and a 6 ml (~1 tsp) blood sample will be taken, to assess how you respond to the heat stress. These sessions should take less than 3 hours to complete.

Hot water therapy sessions: This study will have 2 different groups of research subjects like you. To decide which group you will be in, we will use a method of chance. This method is like flipping a coin or rolling dice. Each group will get slightly different care.

Upon enrolling in the study, you will be assigned to one of two groups: water bathing at 105°F or 97°F in the lab. On days 2-6 and 8-12 of the therapy sessions, you will immerse yourself to a water level at the shoulders for ~30 min, followed by immersion to the hip level for ~60 min (total immersion time of 90 min).

Post-intervention tracking period: after completing the heat therapy sessions, you will be asked to continue to take baths at home once every 4 days for 1 month. During this time, you will be asked to record the intensity and frequency of your hot flashes daily and other menopause-related symptoms weekly. At the end of this month you will be given a final exit survey, in order for you to provide the researchers information about your experience participating in the study.

Throughout the study, the following equipment will be used:

Primary outcomes – hot flash and other menopause-related symptoms:

- Greene climacteric questionnaire: This is a standard questionnaire used to quantify the intensity of 21 common menopause-related symptoms you will be asked to fill out once a week.
- Daily hot flash diary – Based on industry-standard hot flash diaries, this tracks the number and frequency of hot flashes you feel. Our diary also includes measures of morning core temperature and heart rate, as well as immersion time, to track the progress of the heat therapy sessions.
- Exit questionnaire – Further questions for you to complete once at the end of the study in order to gain insight into your subjective experiences using heat therapy and to determine the likelihood you would implement this therapy in your life.

Secondary outcomes – physiological responses to heat stress:

- Expired gas analysis - In your preliminary trial, you will be asked to wear a mask over your nose and mouth. This mask will be connected to a machine that samples your expired breath for oxygen and carbon dioxide. This mask does not interfere at all with your breathing and you will be able to breathe normally throughout the test.
- Esophageal probe - To monitor rapidly changing central (mixed blood) body temperature, a flexible esophageal temperature probe (2 mm in diameter) will be inserted through one of your nostrils.
- Rectal probe – To measure core body temperature, you will be asked to insert a flexible probe though the anus into the rectum (10-12 cm).
- Skin temperature - Eight skin probes that resemble watch batteries will be taped to the skin surface (on the forehead, shoulder, chest, upper right back, forearm, back of the hand, thigh, and calf) with hypoallergenic tape.
- Sweat capsule - Two small plastic capsules (that resemble plastic bottle caps) will be taped to the upper back and forearm. This capsule picks up humidity from the skin and provides a measurement of local sweat rate.
- Skin blood flow - A flexible laser probe will measure skin blood flow non-invasively at the upper back. This measuring device does not result in any discomfort or residual medical effects.
- Blood Pressure - Blood pressure will be measured pre and post exercise using an automatic inflatable cuff around your upper left arm (similar to a normal blood pressure machine).
- Heart rate - Heart rate will be monitored using electrocardiogram by placing five sticky electrodes on your chest. This is the same technique used in hospitals to perform cardiovascular assessments.
- Body weight measurement - You will be weighed on a wide platform scale immediately before the start of exercise and immediately after exercise has been completed.
- Rating of perceived exertion scale - Every five minutes, you will also be asked to rate your level of perceived effort to perform the exercise you are doing verbally on a 14 point scale that ranges from 6 (very very light) to 20 (very very hard).
- Whole body thermal sensation - Every five minutes, you will be asked to report your whole-body thermal sensation scored verbally on a standardized 9-point scale for thermal sensation (ranging from very cold to very hot).
- Whole body thermal comfort - Every five minutes, you will be asked to report your whole-body thermal comfort scored verbally on a standardized 9-point scale for thermal comfort (ranging from very comfortable to very uncomfortable).
- Urine specific gravity – The researchers will also ask you to provide a very small urine sample prior to the start of each study visit. The purpose of this is to ensure that you are properly hydrated.
- Blood sample: In this study we will need to get about 3 total tsp of blood from you. We will get blood by putting a needle into one of your veins and letting the blood flow into a glass tube. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin. We will take a blood sample by a trained member of our research team 3 times total during the study.
- Reproductive hormone levels – If the participant are a female participating in this study, we will also be using a small electronic device to test levels of urinary estrogen, progesterone, and luteinizing hormone from the small urine sample provided prior to the start of each study visit.

Other people in this study: Up to 100 women will participate in this study.

Risks and Discomforts It is likely that you will experience at least some level of discomfort owing to increases in body temperature and the exertion of exercise. You will be informed exactly as to when temperatures will increase and be continuously monitored for your own safety. However if you feel that the level of discomfort is too much please let one of the investigators know immediately and they will work to fix the problem. The potential risks and discomforts that are associated with all of the procedures are very small and detailed below.

Rectal and esophageal probes - Perforation of the rectum or esophagus can theoretically occur during insertion of the temperature probes, potentially causing inflammation and infection. Perforation of the rectum or esophagus is extremely rare and no such incident has ever occurred in any of the five laboratories the principal investigator has worked in, which has involved hundreds of these types of insertions, nor has the principal investigator ever heard of a

perforation occurring in any research lab. The risk of transmission of infectious disease is negligible as each subject has her own sterile probes that will be disposed of after each trial. To further mitigate discomfort, pediatric (i.e. made for children) temperature probes will be used as they are smaller and flexible than those used for adults.

Physical activity/elevations in body temperature - There are some minor physical risks associated with any form of exercise. There is essentially no major risk for people who are able to ambulate without assistance while performing the walking exercise. The speed you will be walking at will be similar to a pace you would encounter in your everyday life. Please notify the researcher if you have a musculoskeletal injury or any concerns about being able to safely walk on a treadmill. During all experimental protocols, you will be under close examination by the investigators. For all experiments, core body temperatures will be monitored continuously measured and the heat therapy or physiological assessment protocol will be immediately terminated if your core temperature reaches 103.1°F (39.5°C). If you become light-headed or dizzy, exercise will be terminated and you will be rapidly cooled in a cold shower next door to the lab, rehydrated with an electrolyte replacement drink (Gatorade, for example) and continuously monitored until your core temperature returns below 38.0°C (100°F).

Arterial and venous occlusion - This research uses the common sphygmomanometer method for measuring blood pressure. As such, some pain and discomfort may be felt when the blood pressure cuff is inflated.

Blood draw: There are risks of pain/discomfort associated with the needle stick in standard blood draw procedures. Additionally, there are less likely risks of bruising and infection at the needle stick site. To minimize these risks, only trained research staff will perform the blood draw procedure and will adhere to bloodborne pathogen and biosafety practices.

Benefits Based on available evidence, we believe that heat therapy will help reduce the intensity of hot flashes and potentially other menopause related symptoms. Therefore, participating in this study might help with your menopause related symptoms, however, this is not guaranteed.

Compensation You will be compensated for your time in the study with a $100 gift card as a thank you gift.

Confidentiality

You will be assigned a subject number so that the researchers can keep your personal information secret. One copy of the key that links your personal information to your subject number will be kept in Dr. Morris' office in a locked cabinet. All physiological data collected will be deidentified and stored on computers protected by passwords.

Your confidentiality will be maintained to the degree permitted by the technology used. Specifically, no guarantees can be made regarding the interception of data sent via the Internet by any third parties.

Certain offices and people other than the researchers may have access to study records. Government agencies and UCCS employees overseeing proper study conduct may look at your study records. These offices include the UCCS Institutional Review Board, and the UCCS Office of Sponsored Programs and Research Integrity. UCCS will keep any research records confidential to the extent allowed by law. A study number rather than your name will be used on study records wherever possible. Study records may be subject to disclosure pursuant to a court order, subpoena, law or regulation.

Additionally, there may be instances where the researcher(s) cannot keep information you provide them confidential, including reports of abuse or neglect of a child, at-risk adult, dependent adult, or elder. If such information is reported to the researcher(s), they may have to report it to the appropriate authorities.

If you would like to report an incident, please contact the Office of Institutional Equity at 719-255-4324 or via email equity@uccs.edu or for additional resources visit their website https://equity.uccs.edu/

Your de-identified data collected during this study could be used for future research studies without additional consent. Also, your de-identified data may be made available to the scientific community in an online format as required by publishers of scientific manuscripts.

Voluntary Participation and Withdrawal from the Study

Taking part in this study is voluntary. You have the right *to* leave a study at any time without penalty. Withdrawal will not interfere with your future care or services at UCCS. You may refuse to do any procedures you do not feel comfortable with, or answer any questions that you do not wish to answer. If you withdraw from the study, you may request that your research information not be used by contacting the Principal Investigator listed above and below.

Contact Information

Contact (PI's info): Dr. Morris – nmorris6@uccs.edu

- if you have any questions about this study or your part in it,
- if you have questions, concerns or complaints about the research, or
- if you would like information about the survey results when they are prepared.

Contact the Research Compliance Program Director at 719-255-3903 or via email at irb@uccs.edu:

- if you have questions about your rights as a research participant, or
- if you have questions, concerns or complaints about the research.

Consent

A copy of this consent form will be provided to you.

Are you interested in being contacted about future research I may conduct? ☐ Yes or ☐ No.

The University of Colorado Colorado Springs is not able to offer financial compensation nor to absorb the costs of medical treatment should you be injured as a result of participating in this research.

I understand the above information and voluntarily consent to participate in the research. By signing this consent, I am confirming that I am 18 years of age or older.

Signature of Participant _____ Date _____