U.S. Army Research Institute of Environmental Medicine

CONSENT TO PARTICIPATE IN RESEARCH

Title of Protocol: The effects of cocoa-rich bioflavanol supplementation on manual dexterity during cold exposure (Cold Induced Vasodilation)

Principal Investigator: Billie K. Alba, Ph.D.

Funding Source(s)/Sponsor: Defense Health Program, Department of Defense (DoD)

INTRODUCTION

You are asked to participate in a research study conducted at the U.S. Army Research Institute of Environmental Medicine (USARIEM) by Billie Alba. You are being asked to be in this research study because you are a healthy Soldier or civilian between the ages of 18-49 and the Army needs to develop solutions that allow Soldiers to function and use their hands better in a cold environment. We are recruiting up to 25 people so we can collect complete data on 20 people (10 men and 10 women). The study will take place at USARIEM in Natick, MA.

Your participation in this research is voluntary. It is important that you read what is written below, and ask questions about anything you do not understand. You may want to talk with your family, friends, or others to help you decide if you want to be part of this study. When you feel that your questions have been answered, you will be asked if you agree to be part of the research or not. If you agree, you will be asked to sign this consent form. You will be given a copy of this form to keep.

WHY IS THIS RESEARCH BEING DONE?

The purpose of this research is to develop a new way for Soldiers to keep their hands warm and functional in a cold weather environment. The main purpose of this experiment is to see if finger temperatures can be maintained throughout 30 minutes of cold water immersion when a nutritional supplement made from chocolate is eaten. This chocolate contains high amounts of flavanols, compounds which are believed to improve blood flow. We don't know if it can improve blood flow and temperatures to the hands and fingers in the cold. Another purpose is to see if these flavanol compounds can change the types of bacteria in your gut.

ELIGIBILITY

You may take part in this research study if all of the following applies to you:

- Are 18-49 years old (17 year olds on active duty are allowed).
- Willing to refrain from eating things like cocoa, chocolate, apples, red, white, and sweet wine, apricots, blueberries, peaches/nectarines, plums, grapes, strawberries, pecans (no more than ½ cup/day), pistachios (no more than ½ cup per day), apple juice, yogurt, kefir, aged cheese, kombucha, sour cream, pickles, sauerkraut, tempeh, kimchi, miso, vinegar, sourdough bread, and beer for 2 weeks before and during the study.
- Willing not to change your daily intake of tea (green or black) or coffee.

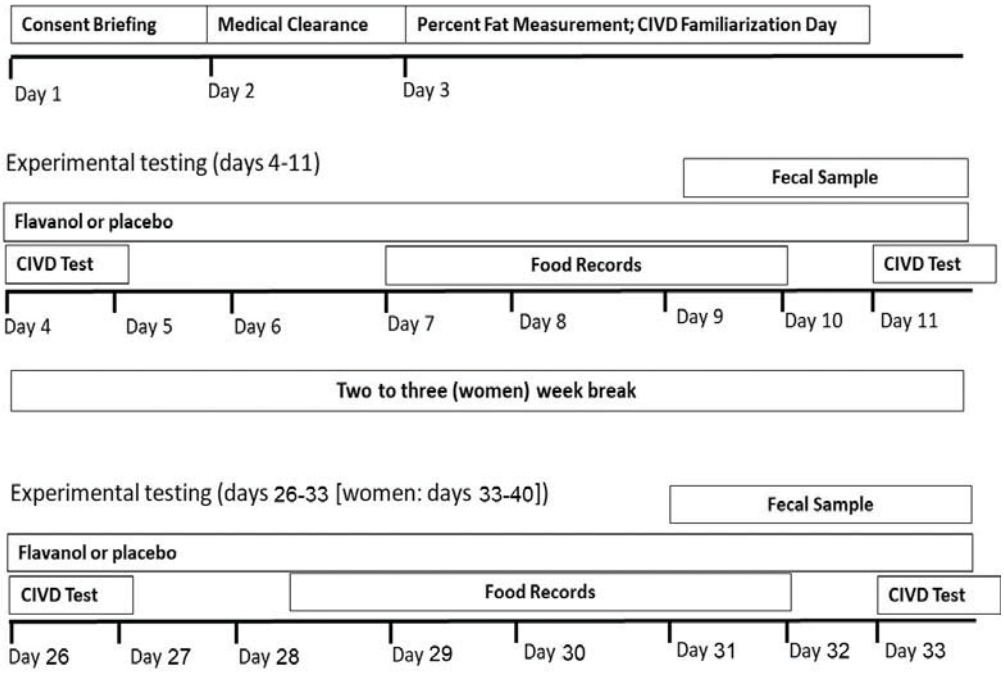
You should not participate in this study if any of the following applies to you:

- Have a history of cold injuries.
- Have been diagnosed with Raynaud's syndrome.
- Have been diagnosed with cold-induced asthma
- Have difficulty swallowing pills.
- Have previous hand/finger injuries that impair hand function.
- Have metal hardware (plates/screws) in the forearms and hands.
- Have donated blood in the last 8 weeks.
- Take any medicine (including any over the counter medication such as Tylenol, Advil, Sudafed, etc.), with the exception of birth control and a multivitamin.
- Have known allergies to medical adhesives or cocoa/chocolate.
- Have a history of gastrointestinal disease; or previous gastrointestinal surgery.
- Have a planned MRI during the study or within 2 days after completing a cold test.
- If you plan to exercise or smoke within 8 hours of testing.
- Are pregnant or breastfeeding.
- Have taken oral antibiotics within 3 months of study participation.
- Are unable to refrain from the consumption of fermented food/pre and probiotic products for 2 weeks prior to and throughout study participation.
- Have had a colonoscopy within 3 months of study participation.
- On average have a bowel movement less frequently than every other day.

WHAT WILL HAPPEN DURING THIS RESEARCH?

If you agree to participate in this research, you will be asked to do the following things:

Place your middle finger into cold water (39°F) for 30 minutes. This is called a cold-induced vasodilation test (CIVD). There are four cold water immersions over the duration of the experiment. One cold finger immersion will happen a few hours after you take a nutritional supplement called a flavanol. This supplement comes from chocolate and is in pill form. The second cold test will happen a week after the first one after you have taken the flavanol supplement for 8 straight days. The other 2 cold tests will happen after you ingest a placebo (a pill that should not have any effect on the body and is sometimes called a "sugar" pill). Similar to the supplement, you will have a cold finger test after ingesting the placebo on the first day and again a week later. This experiment is a double blind study, which means that neither you nor the research staff will know whether you are getting the flavanol or a placebo. In case there is an emergency, there is a way to find out whether you are getting the flavanol supplement or the placebo. The total amount of time required is different depending on whether you are a man or a woman. For men, the total time is ~33 days, which includes a 2-week time period between taking the flavanol and placebo treatments, so that any extra flavanols can leave your body. For woman, the total time will be ~40 days. The reason is that we need to test women in the first part of their menstrual cycle, about 2-4 days after their period and then again 8 days later. All testing will take place at USARIEM in an environmental chamber. Below is a timeline of test days.



Flavanol Supplement

The flavanol supplement will be given as pills. It is available as a commercial nutritional supplement product and is made by Mars, Inc. The product is called CocoaVia®. You will ingest 900 mg per day of the flavanol (as 4 pills). This supplement was not reviewed or evaluated by the FDA, and does not require review or approval when used as it will be in this study. The placebo will also be given as pills. As mentioned above, you and the research team will not know if you are getting the flavanol or placebo. You will always take the supplement pills about 1 hour after you eat breakfast.

Preliminary measurements

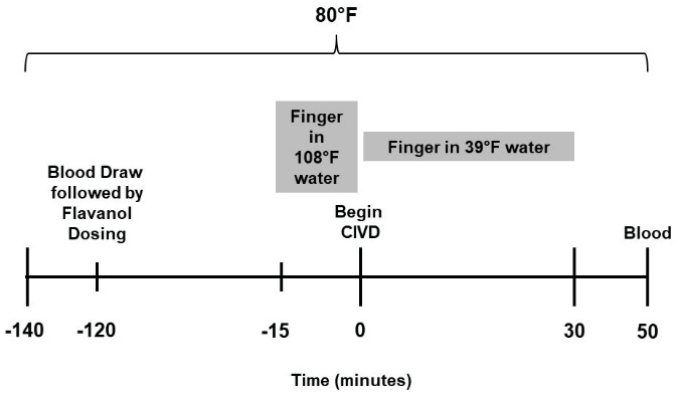
We will measure height and weight and record your age. We will measure your percent body fat by pinching seven different areas on your skin. For woman volunteers, we will test to make sure you are not pregnant. We will have you complete a urine pregnancy test within 72 hours of your first test day of taking the flavanol and placebo pills.

Before testing begins, we will have you put your finger into 39.2°F water so that you know what it will feel like on a regular experiment day.

CIVD Test

On 4 different occasions, you will place your middle finger into 39.2°F water for 30 minutes. We will measure your finger temperature during this time. One CIVD test will happen after you ingest the flavanol/placebo and the other after having ingested the flavanol or placebo for 8 straight days (which includes the first day). The figure below shows the timeline of a CIVD test day. After sitting quietly for 20 minutes, we will take a blood sample, followed by you taking the supplement or placebo. For 15 minutes, you will put your finger into 107.6°F water. After this you will put your finger into 39.2°F water for 30 minutes. We will measure your skin temperatures during this time as well as your deep body temperature. After you take your finger

out of the cold water, you will sit quietly and then another blood sample will be taken. This test will take place in a chamber that will be kept at 80°F.



Cold Water Finger Immersion Physiological Measurements

- Your internal body temperature will be measured continuously using a temperature pill that you will place as a suppository. You will insert the pill before testing and it will be checked before testing. The pill sends a signal to a monitoring device which displays the pill temperature. We will instruct you on how to place the pill.
- Your skin temperature will be measured continuously by sensors taped to your skin in 10 places (back, forearm, tricep, calf, thigh, top of foot, chest, top of hand, in finger nailbed, and on finger pad) throughout the experimental time period. If you have a lot of body hair, these sites may need to be shaved so that the sensors have good contact with your skin.
- Blood pressure and heart rate will be measured every 5 minutes throughout cold water immersion.

Blood draws

You will have a total of 8 blood draws. These blood draws will be taken before and after each cold test. The total amount of blood that we will draw from you will be 23 teaspoons (112 ml). We will take blood samples by putting a needle into a vein of your arm; this is called venipuncture. This is the standard method used to obtain blood for tests. Approximately 3 teaspoons (14 ml) of blood will be removed each time. You will feel slight pain and discomfort when the needle goes into the vein. A bruise may form at the site, but this will gradually disappear. Sometimes the technicians will miss a vein or not get enough blood for the test. They may ask to repeat the venipuncture on a different vein in your arm. You have the right to refuse these repeat attempts. USARIEM policy requires that a senior technician be called in if a technician misses more than two times. The senior technician may repeat the venipuncture up to two additional times. After four unsuccessful attempts, OMSO will be called in to observe any further attempts. To reduce the risks associated with this procedure, it will be performed by a skilled, credentialed technician."

Poop Collection

We will ask you to collect your poop in a special collection container 2 separate times during the study. You will be given detailed instructions on how to collect a poop sample and the supplies needed to do it. We will use your poop to identify the types of bacteria that are present in your gut.

Diet Recording

We will ask you to write down all the foods and beverages that you eat or drink for 4 days on two separate occasions during the study. We will teach you how to record your food and beverages, both by talking to you and giving you written instructions, and will meet with you to review your food records.

WHAT ARE THE POTENTIAL RISKS AND DISCOMFORTS FROM BEING IN THIS RESEARCH?

Below is a list of potential risks and discomforts from being in this study. Each day that you ingest the CocoaVia®, you will be asked how you feel afterwards (stomach upset, nausea) by the medical staff and fill out a questionnaire. If you experience these symptoms, please report them to the staff. You may withdraw from the study if the supplement or placebo makes you feel unwell.

Source of Risk:	Risk:	How we minimize risks:
Cold Water Exposure	• Cold intolerance (pain, numbness, stiffness, swelling, aching, discoloration)	• Small percentage of population experience these symptoms (5 percent) • Symptoms are only temporary until fingers are rewarmed
CocoaVia® Ingestion	• Nausea/GI distress • Headache • Insomnia • Allergy	• Will be medically screened to see if chocolate causes these issues in you • Eat breakfast ~ 1-2 hours before CocoaVia® Ingestion
Core Temperature Pill	• Damage to rectal membrane	• Instructions and lube provided for self-insertion
Blood Draw	• Pain, skin irritation • Dizziness, fainting • Bruising • Infection	• Venipuncture only performed by credentialed staff members • Proper and sterile techniques used
Test Equipment	• Electric shock	• All electronic test equipment is operated by trained personnel • All equipment is inspected for electrical safety prior to use
Adhesives	• Skin irritation	• Excluded if you have an adhesive allergy • Skin properly cleaned and monitored

Risks Associated with Loss of Privacy and Breach of Confidentiality

Your Social Security number may be needed for payment. If we have your social security number, we will keep it locked up. When your study participation is over, we will submit the paperwork for payment and destroy your link to your social security number. Please see below for other ways we will protect your privacy and reduce the risk of a breach of confidentiality.

WHAT ARE THE POSSIBLE BENEFITS FROM BEING IN THIS RESEARCH?

There are no benefits to you for participating in this study. The overall benefit of this study is the information gained may lead to the development of a product or countermeasure that helps Soldiers maintain manual dexterity and better able to complete tasks during cold-weather operations.

WHAT ALTERNATIVE OPTIONS TO PARTICIPATION ARE AVAILABLE TO ME?

The only alternative to participating in the research is to not participate

WILL I HAVE TO PAY FOR ANYTHING IF I TAKE PART IN THIS RESEARCH?

If you do not reside on the Natick Soldier Systems Center, you will be responsible for your travel costs to and from the base.

WILL I BE PAID TO TAKE PART IN THIS RESEARCH?

All volunteers (Soldier and civilian) may receive $50.00 for each blood draw. There are a total of 8 blood draws so that a total of $400.00 may be paid to you over the duration of the study. Your social security number will be needed to process your payment, as required by law. This information will be carefully protected; only the PI will have access to your social security number. Total payments of $600 or more within one calendar year will be reported by the Defense Finance and Accounting Service to the Internal Revenue Service (IRS). This may require you to claim the compensation that you receive for participation in this study as taxable income.

WHAT HAPPENS IF I AM INJURED AS A RESULT OF TAKING PART IN THIS RESEARCH?

If at any time you believe you have suffered an injury or illness as a result of participating in this research, please contact Dr. Alba at Office Phone: 508-206-2171; Cell Phone: 352-316-5023; or e-mail: billie.k.alba.civ@mail.mil

If you are injured because of your participation in this research and you are a DoD healthcare beneficiary (e.g., active duty military, dependent of active duty military, retiree), you are entitled to medical care for your injury within the DoD healthcare system, as long as you remain a DoD healthcare beneficiary. This care includes, but is not limited to, free medical care at Army hospitals or clinics.

If you are injured because of your participation in this research and you are not a DoD healthcare beneficiary, you are entitled to medical care for your injury at an Army hospital or clinic; medical care charges for care at an Army hospital or clinic will be waived for your research-related injury. You are also entitled to care for your injury at other DoD (non-Army) hospitals or clinics, but care for your injury may be limited to a given time period, and your insurance may be billed. It cannot be determined in advance which Army or DoD hospital or clinic will provide care. If you obtain care for research-related injuries outside of an Army or DoD hospital or clinic; you or your insurance will be responsible for medical expenses.

For DoD healthcare beneficiaries and non-DoD healthcare beneficiaries: Transportation to and from hospitals or clinics will not be provided. No reimbursement is available if you incur medical expenses to treat research-related injuries. No compensation is available for research-related injuries. You are not waiving any legal rights.

HOW WILL YOU PROTECT MY PRIVACY AND THE CONFIDENTIALITY OF RECORDS ABOUT ME?

The principal investigator will keep records of your participation in the research. To protect your privacy, any of your research-related records (including blood, feces, temperature

responses) will be labeled or "coded" with an assigned research participant number that will not include your name or social security number. Dr. Alba will keep the link between your participant number and your research records in a locked cabinet in her office. Dr. Alba is the only person who will be able to match your research participant number with any of your personal identifying information. The link between your name and participant number will be destroyed when Dr. Alba closes the protocol. All the study data that we get from you will be kept locked up or in password-protected computer files.

When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity to others. If you sign the photo release form, we may use your picture in presentations, but we will not link any of your data directly with a picture. These pictures are used to help describe the testing conditions.

Authorized representatives of the following groups may need to review your research and/or medical records as part of their responsibilities to protect research participants:

- US Army Medical Research & Development Command Institutional Review Board
- US Army Human Research Protections Office and other DOD offices charged with oversight of human research
- US Army Research Institute of Environmental Medicine, Office of Research Quality and Compliance
- *US Army Research Institute of Environmental Medicine, Office of Medical Support and Oversight (OMSO)*

Complete confidentiality cannot be promised for military personnel, because information bearing on your health may be required to be reported to appropriate medical or command authorities.

WHAT IF I DECIDE NOT TO PARTICIPATE IN THIS RESEARCH?

Your participation in this research is voluntary. You may decline to participate now or stop taking part in this research at any time without any penalty or loss of benefits to which you are entitled. You may withdraw from the study if the supplement or placebo makes you feel unwell. Deciding not to participate now or withdrawing at a later time does not harm, or in any way affect, your current or future relations with this institute, your superiors, or the U.S. Army. If you do not complete the study, we will still use the data we have collected and analyze your samples. You will be paid for the total number of blood draws that you have completed.

WHAT COULD END MY INVOLVEMENT IN THE RESEARCH?

- We ask that you follow the directions to the best of your ability.
- If you are unable to do so, or the researchers feel it is best for you to leave the study, the researchers may end your participation in the study even though you might like to continue.
- The researchers may have to withdraw you from the study if you become ill or injured during the research.
- The decision may be made either to protect your health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate. The investigator will make the decision and let you know if it is not possible for you to continue.

WHAT IF ANY NEW INFORMATION IS FOUND OUT?

During the course of the research, the investigators will tell you of any new findings that might cause you to change your mind about continuing in the study. If new information is provided to you, the investigators will obtain your consent to continue participating in this study.

WHAT HAPPENS WITH THE DATA AND SPECIMENS BEING COLLECTED?

Your data are valuable and will be kept indefinitely, without any link to your identity, for use in other research studies and may be shared with other researcher(s). Blood samples will be kept until all planned analyses are completed, and resulting publications have been accepted to peer-reviewed journals. Fecal samples will be analyzed for current planned analyses. Archived fecal samples (de-identified) will also be saved for possible future research and may be shared with other institutions. If you would like a copy of the final report/publication when the study is complete, please contact Dr. Alba at 508-206-2171 or billie.k.alba.civ@mail.mil for a copy.

VOLUNTEER REGISTRY DATABASE

It is the policy of the U.S. Army Medical Research and Development Command (USAMRDC) that data sheets are to be completed on all volunteers participating in this greater than minimal risk research for entry into the command Volunteer Registry Database. The information to be entered into this confidential database includes name, address, social security number, study name, and dates. The intent of the database is two-fold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRDC; and second, to ensure that the USAMRDC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRDC for a minimum of 75 years.

WHO SHOULD I CALL IF I HAVE QUESTIONS OR CONCERNS ABOUT THIS RESEARCH?

If you have questions about the research at any time, you should contact:
Billie Alba. Office phone: 508-206-2171; Cell Phone: 352-316-5023;
e-mail: billie.k.alba.civ@mail.mil

If you believe you may have a research related injury or illness, please, if during duty hours, immediately contact Dr. Alba at 508-206-2171 or the USARIEM Office of Medical Support & Oversight (508-206-2265). Outside of duty hours, please call Dr. Alba at 352-316-5023.

If you have questions regarding your rights as a research participant, you may contact the HQ USAMRDC IRB Office at 301-619-6240 or by email to usarmy.detrick.medcom-usamrmc.other.irb-office@mail.mil. You may also contact the USARIEM Office of Research Quality and Compliance at (508) 206-2371 or by email to usarmy.natick.medcom-usariem.mbx.usariem-rqc-protocol@mail.mil.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. The web site will not include information that can identify you. At most the web site will include a summary of the results. You can search this website at any time.

SIGNATURE OF RESEARCH PARTICIPANT

I have read the information provided above. I have been given an opportunity to ask questions and all of my questions have been answered to my satisfaction.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date