**Informed Consent Document**

Gut microbiota targeted nutritional intervention for gut barrier integrity at high altitude

NCT04111263

United States Army Research Institute of Environmental Medicine (USARIEM)

# CONSENT TO PARTICIPATE IN RESEARCH

Title of Protocol: Efficacy of a gut microbiota-targeted nutritional intervention for promoting gut barrier integrity during short-term exposure to hypobaric hypoxia

Short Title: Fiber and polyphenols for promoting performance at high altitude

Principal Investigator: J. Philip Karl, PhD, RD

You are being asked to participate in a research study. As you think about your decision, you should consider all of the information included in this informed consent form. The table below summarizes **key** things about the research. After reading the summary, if you are interested in participating, read the rest of this consent form for more details about this study.

| RESEARCH SUMMARY | |
|---|---|
| **Voluntary Participation** | You do not have to take part in this research. It is your decision. You can also choose to stop participating at any time during the study. |
| **Purpose** | We want to determine whether supplementing your diet with fiber and plant-based nutrients called polyphenols will help healthy bacteria in your intestines grow, improve intestinal, brain and immune function at high altitude, and change your metabolism at high altitude. Results from this study will be used to help combat ration developers design new foods for improving the performance of Warfighters operating at high altitude, and possibly other environments. |
| **Duration** | You will be in this study for about 10 weeks. During that time you will participate in about 173 total hours of study-related activities. |
| **Procedures** | While you are in the study, you:<br>• Will be on a strict, provided diet for about 4 (non-consecutive) of the 10 weeks which will mostly consist of Meal, Ready-to-Eat (MRE) military ration products.<br>• Will not be allowed to smoke (including e-cigarettes), vape or chew tobacco during the 4 weeks of eating the provided diet.<br>• Will not be allowed to drink alcohol or consume caffeine during the 4 weeks of eating the provided diet.<br>• Will eat study snack bars daily for about 6 of the 10 weeks.<br>• Will “live” in an altitude chamber with up to 5 other participants for about 40 hours on 3 separate occasions.<br>• Will collect your own poop 12 separate times using a provided kit.<br>• Will have blood, urine, and saliva, and tears collected from you on multiple occasions. (Tear collection will not occur while COVID-19 risk reduction procedures are in place).<br>• Will swallow an electronic pill that measures how fast things move through your intestines 3 separate times. |

| | |
|---|---|
| **Procedures** continued | While you are in the study, you:<br>• Will not be allowed to take dietary supplements or eat foods containing live bacteria (like yogurt).<br>• Will not be allowed to take non-steroidal anti-inflammatory medicines like aspirin or ibuprofen. |
| **Drugs/Devices** | The devices used in this study are FDA-approved monitors for measuring how fast food moves through your intestines, heart rate, blood oxygen, the amount of oxygen you breathe, activity/sleep, and vigilance/attention. |
| **Risks** | The **main** risks from being in this study are:<br>• Altitude illness (acute mountain sickness) from living in the altitude chamber<br>• Muscle fatigue and soreness from the exercise<br>• Bruising and swelling from the needles used to draw blood<br>• Bloating, gassiness, cramping from the change in diet and study snack bars<br>• COVID-19 transmission (see "Special Note Regarding COVID-19 below") |
| **Benefits** | There is no direct benefit to you, but we hope that results from this study will help the Army determine changes it can make to its combat rations in order to help Soldiers perform better at high altitudes. |
| **Alternatives** | The only alternative to you is to simply not participate in the study. |
| **Payment** | You will be paid for your participation in this study. |

**Special Note Regarding COVID-19**

The COVID-19 pandemic means that you are potentially at risk of contracting a serious illness any time you interact with another person. To reduce risk of exposure, certain study activities will be added or changed if necessary based on current health guidelines. For example, we will ask you to wear personal protective equipment (PPE) such as face coverings/masks and practice social-distancing whenever possible. These changes (known as "risk reduction procedures") are described in the sections below.

**INTRODUCTION**

You are asked to participate in a research study conducted at the United States Army Research Institute of Environmental Medicine (USARIEM) by J. Phillip Karl, Ph.D., R.D., and other researchers from USARIEM, the Combat Capabilities Development Command-Soldier Center (CCDC-Soldier Center), the Walter Reed Army Institute of Research (WRAIR) and the University of Reading. You are asked to participate in this research because you are a healthy, physically active adult.

You do not have to take part in this research. It is your choice whether or not you want to participate. It is important that you understand this research study so that you can make a decision. This decision process is called informed consent. To make your decision, you will

need to consider all of the information provided here 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?

Most people, including Warfighters, who travel to high altitude (mountainous) regions feel sick and have fuzzy thinking until their body can adjust to the new environment. Those effects might be related to changes in intestinal function. One potential way of reducing or preventing these things from happening at high altitude is by feeding bacteria that live in our intestines. These bacteria play an important role in our health by helping us digest nutrients, strengthening our immune systems, and keeping our intestines healthy. These bacteria like to live off of nutrients that we do not digest. Some of these nutrients, known as fiber and polyphenols, come from plant foods and promote healthy bacteria. In this study, we will determine whether supplementing your diet with fiber and polyphenols will promote healthy bacteria, improve intestinal, brain and immune function, and change chemical processes in the body, called metabolism, at high altitude. We will also determine if these nutrients impact markers of bone health. We will also use samples collected from this study in laboratory experiments designed to help better understand how different nutrients and bacteria interact. Results from this study will be used to help combat ration developers design new foods for optimizing the performance of Warfighters operating at high altitude, and possibly in other stressful environments.

## WHAT WILL HAPPEN DURING THIS RESEARCH?

If you agree to participate in this research, you will be asked to do the following things (see Tables 1 and 2 below):

**Table 1.** Overview of study schedule. All study visits will take place at USARIEM or an alternate location at the Natick Soldier Systems Center. COVID-19 risk reduction procedures will be followed as necessary based on current health guidelines.

| Phase | Week | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
|---|---|---|---|---|---|---|---|---|
| **Baseline (BL)*** | | 2-4 laboratory visits (60-~180 min each); screening & baseline testing | | | | | | |
| **Diet supplementation Phase 1** | **1** | 5 laboratory visits (30-~180 min each); practice testing; eat 2 snack bars/day<br>*COVID-19 risk reduction: 3 laboratory visits, 2 video calls* | | | | | | |
| | **2** | Daily laboratory visits (~60min);<br>Eat provided diet + 4 snack bars/day | | | | | **Altitude Chamber ~40 hours** | |
| **Washout** | **3** | *3-4 laboratory visits (<60min); days 1 & 2 only: Eat provided diet* | | | | | | |
| **Diet supplementation Phase 2** | **4** | 5 laboratory visits (~30 min each); eat 2 snack bars/day<br>*COVID-19 risk reduction: 2 laboratory visits, 3 video calls* | | | | | | |
| | **5** | Daily laboratory visits (~60min);<br>Eat provided diet + 4 snack bars/day | | | | | **Altitude Chamber ~40 hours** | |
| **Washout** | **6** | *3-4 laboratory visits (<60min); days 1 & 2 only: Eat provided diet* | | | | | | |

| | | | |
|---|---|---|---|
| **Diet supplementation Phase 3** | **7** | 5 laboratory visits (~30 min each); eat 2 snack bars/day<br>*COVID-19 risk reduction: 2 laboratory visits, 3 video calls* | |
| | **8** | Daily laboratory visits (~60min);<br>Eat provided diet + 4 snack bars/day | **Altitude Chamber ~40 hours** |
| **Washout** | **9** | *2-3 laboratory visits (<60min); days 1 & 2 only: Eat provided diet* | |

*Baseline activities may occur over >7 days if needed.

**Screening and baseline testing (Week 0)**

***Screening:*** Before the start of the baseline testing, we will ask you to complete a medical screening with USARIEM medical staff. You will be asked questions about your medical history, and will have a small amount of blood drawn (less than 1 tablespoon) to determine if you are healthy enough to participate in this study. Your height and weight will be measured. During screening, you will also be asked to fill out a questionnaire which will ask about you (for example, age, race, education level) and about the eligibility criteria listed below. Screening will take place over 1 or 2 visits to USARIEM and will take about 2 hr. If you pass screening, we will ask you to continue in the study by starting baseline testing.

Any health problems found during the screening process will be documented, and you will be provided a copy. You will be encouraged to make an appointment with your doctor to follow up with a full evaluation of the identified health concerns.

***Baseline testing (see Table 2 for details of study procedures):*** Prior to baseline testing we will ask you to stop taking and to not consume any of the following products throughout your study participation: Non-steroidal anti-inflammatory medications (for example, aspirin, Advil, Aleve); antihistamine medications; probiotic-containing foods (for example, yogurt, kefir); and dietary supplements including prebiotic and probiotic supplements. *Please ask a study team member if you have questions about any of these restrictions.*

During baseline testing you will be asked to complete diet and activity records for 3 days in a row. This requires writing down everything you eat and drink, and your physical activity during that time. You will also wear an activity monitor (similar to a watch) for these 3 days. You will also complete a fitness test on a treadmill, and provide a poop sample during baseline testing.

**Orientation (Baseline-week 1; *see Table 2 for details of study procedures):***
Over the course of baseline testing and study Week 1, you will complete several tasks to help you become familiar with the tests that will be performed later during the study. These tasks will include completing questionnaires, measurement of your body weight and resting metabolism, medium-intensity exercise on a treadmill, and completing computer tests that assess your cognition. These tasks will be completed during 3 separate visits to the laboratory which will take about 180 min each visit.

**Diet-supplementation (Weeks 1-2, 4-5, 7-8; *see Table 2 for details of study procedures):***
During the first week of each phase (Weeks 1, 4, and 7), you will visit the lab 5 times each week for about 30 minutes. Your body weight will be measured and you will consume two study snack bars (see below). You will complete questionnaires asking about how you feel and your appetite. Additional snack bars will be provided for you to consume on non-lab days.

**Note: While COVID-19 risk reduction procedures are in place, labs visits will be reduced to 3 times per week for Week 1 and 2 times per week for Weeks 4 and 7. On non-lab days (excluding most weekends), you will be asked to participate in a video call with staff members (with Facetime, WhatsApp, or similar) while you are eating the study bars and completing study questionnaires.**

During the first 5 days of the second week of each phase (Weeks 2, 5, and 8), you will visit the laboratory twice daily to eat breakfast, lunch, and 4 study snack bars. Dinner and any additional snacks will be provided to you to eat at home. We will measure your body weight and you will complete questionnaires asking about how you feel and your appetite. We will collect a poop sample from you on the 4$^{th}$ day (or the 5$^{th}$ day if you do not produce a sample on the 4$^{th}$ day). On one day you will also complete computer tests that measure cognition. You will wear a sleep/activity monitor on your wrist for all 5 days. Total visit time during these 5 days will be about 60 minutes/day.

*Please note that all of your food and beverages will be provided to you during Weeks 2, 5, and 8, and the first 2 days of Weeks 3, 6, and 9. We will feed you enough to maintain your body weight, and will ask you to eat and drink everything that we give you and nothing else (except water).* The foods provided will consist mainly of Meals, Ready-to-Eat rations (known as MREs), and the study snack bars. During this time you will not be allowed to eat or drink caffeinated products or alcohol. You will also not be allowed to use nicotine-containing products. (You are allowed to consume caffeine, alcohol, and nicotine-containing products at other times of the study).

On day 6 of Weeks 2, 5 and 8, you will visit the laboratory early in the morning and enter into the USARIEM altitude chamber where you will stay for about 40 hours (days 6 and 7, 1 overnight). We will provide you with food and beverage, and you will eat 4 study snack bars each day. You will participate in several study activities on both days you are in the altitude chamber. These tasks include having your body weight and resting metabolism measured, 60 minutes of medium-intensity exercise, completing computer tests assessing your cognition, completing questionnaires asking about how you feel and your appetite, 2 blood draws each day, and tear and saliva collection. You will also wear an activity/sleep monitor on your wrist, and a "vigilance monitor" on your wrist while in the chamber. **Note: While COVID-19 risk reduction procedures are in place, tear collection and resting metabolism measurements during weeks 2, 5 and 8 will not occur, and you will be tested for COVID-19 before entering the chamber.**

In addition to the tests noted above, 2 additional measurements will begin on day 6 of Weeks 2, 5, and 8. We will measure how leaky your gut is by having you drink two different sugar substitutes (sucralose and erythritol) mixed in water, and collecting all the urine you produce for the next 24 hours. You will also be asked to swallow a SmartPill which will measure how fast food moves through your intestines. On day 7 of Weeks 2, 5, and 8 we will also collect a poop sample. You will be released from the altitude chamber the night of day 7.

**Washout (Weeks 3, 6, 9)**

After leaving the altitude chamber on day 7 of Weeks 2, 5 and 8 you will continue to eat food and beverages provided to you and nothing else (except water) for 2 days. On the second day we will ask you to complete computer tests to measure your cognition, and to provide another

poop sample. If you do not provide a sample, we will ask you to continue on the study diet until you do. We will also ask you to provide a second poop sample on day 6 of Weeks 3 and 6.

**Table 2:** Description and timing of study procedures

| Procedure | Description | Study time point |
|---|---|---|
| Diet and activity records | You will record everything you eat and drink, and your physical activity for 3 days in a row. This will help us determine how much to feed you during the study. | Week BL (3 days) |
| Fitness test | Your fitness will be determined on a treadmill, while wearing a heart rate monitor and breathing through a mouthpiece or rubber face mask connected to a machine that measures your breathing. The heart rate monitor is held in place using an elastic band that fits around your chest, and tells us how hard your heart is working. You will be asked to run at an incline until you can't run any more. The result will be used to better estimate how hard you need to exercise during moderate-intensity exercise (see below). This test takes about 30 minutes. | Week 0 (1 day) |
| Computer testing | You will be asked to complete several tests on a computer which will measure your cognition (for example, memory, attention, reaction time, reasoning, risk-taking behavior). You will complete some of these tests before, during, and after you exercise. Depending on the time point, these tests will take about 15-45 minutes to complete. | Weeks BL-1, (3 days, multiple times);<br><br>Weeks 2, 5, 8 (3 days, multiple times)<br><br>Weeks 3, 6, 9 (1 day) |
| Sleep/activity monitor | We will track your sleep and activity during baseline testing, and during the second week of each diet supplementation phase by asking you to wear a lightweight device on your wrist (similar in size to a wristwatch). The device contains sensors that measure the environment and your activity. | Weeks BL, 2, 5, 8 (7 days) |
| Vigilance monitor | We will measure your vigilance (attention) during baseline testing and then when living in the altitude chamber. You will wear a lightweight device on your wrist (similar in size to a wristwatch). The device will be programmed to vibrate or sound a tone at different times of the day which will require you to push a button to stop. This will not be active while you are sleeping. | Weeks BL, 3, 6, 9, (2 days);<br><br>Weeks 2, 5, 8 (2 days) |

| | | |
|---|---|---|
| Medium-intensity exercise | You will walk or jog slowly on a treadmill for 60 minutes. You will wear a heart rate monitor on your chest and at times breathe through a mouthpiece or rubber face mask connected to a machine that measures your breathing. During this test we will also measure the amount of oxygen in your blood by attaching a small, painless clip known as a pulse oximeter to the end of your finger. | Weeks BL-1, (2 days);<br><br>Weeks 2, 5, 8 (2 days) |
| Resting metabolism | We will measure your breathing by placing a clear plastic bubble attached to a tube over your head while you lay awake for about 30 minutes. This test will tell us how many calories you normally burn while resting, and will happen early in the morning after not eating for at least 8 hours.<br>**Note: While COVID-19 risk reduction procedures are in place, this measurement will only occur once during BL or Week 1.** | Weeks BL, 1, 2, 5, 8, (1 day) |
| Poop sample collection | We will collect 12 total poop samples from you to identify the types and activities of bacteria that are present in your intestines, and to determine how different nutrients influence the growth and activity of these bacteria. You will be given detailed instructions on how to collect a sample and the supplies needed to do it. This may require transporting samples from your home to the laboratory. We will provide supplies for transporting samples. | Weeks BL, 9 (1 day);<br><br>Weeks 2, 3, 5, 6, 8 (2 days) |
| SmartPill | We will use the SmartPill to measure the time it takes for food to pass through your intestines. The SmartPill is a FDA-approved wireless pill similar in size to a large multi-vitamin pill. The SmartPill contains sensors that measure temperature, pressure, and acidity. The pill will move through your intestines while transmitting data to a receiver kept near the body. During each measurement you will swallow one sterile SmartPill under staff supervision. For most people the SmartPill will leave the body within 24-48 hr. You will wear a bracelet indicating the pill is inside of you until elimination from the body is confirmed by study staff by looking at changes in the temperature readings (when the SmartPill hits toilet water, the temperature will drop). | Weeks 2, 5, 8; (1 day) |
| Gut leakiness | You will drink water mixed with two types of sugar substitutes commonly used in foods and beverages (sucralose and erythritol). We will collect all the urine you produce over the next 24 hours in a jug and measure the amount of sucralose and erythritol in the urine as an indicator of gut leakiness. These urine samples may also be used to measure gut bacteria metabolic activity. | Weeks 2, 5, 8; (1 day) |
| Urine sample | You will collect a urine sample in a sterile cup at home immediately after waking up on the mornings you are going to begin living in the altitude chamber. These samples will be used to measure your hydration level, gut bacteria metabolic activity, and your metabolism. | Weeks 2, 5, 8; (1 day) |

| | | |
|---|---|---|
| Tear fluid collection | We will sample tear fluid from the corner of your eye using a small, thin tube called a micropipette. This is a noninvasive procedure that will be used to measure your immune function. The procedure takes about 5 min.<br>**Note: While COVID-19 risk reduction procedures are in place, tear fluid collection will not occur.** | Weeks 2, 5, 8; (2 days) |
| Saliva collection | We will collect your saliva by having you place two small sponges under your tongue for about 3 minutes per sponge. This will help us measure your immune function. | Weeks 2, 5, 8; (2 days) |
| Blood sample collection | We will collect blood from you 12 separate times during the entire course of the study. Over the entire study we will collect about 231 mL (about 16 Tablespoons or 1 cup) of your blood. Blood samples will be collected by trained study staff from one of the veins in your arm by using a small needle attached to a tube. These samples will be used to measure markers of gut health, gut bacteria metabolic activity, inflammation, immunity, stress, metabolism, and bone health. | Weeks 2, 5, 8; (2 days) |
| Questionnaires | You will be asked to complete short questionnaires frequently throughout the study. These questionnaires will ask about your personality, how you feel, and your appetite. | Most study visits, some via video call |
| Pregnancy test (females only) | On the mornings you begin altitude chamber testing, you will perform a urine pregnancy test to make sure that you are not pregnant and that it is safe for you to participate in the study. | Weeks 2, 5, 8; day 6 |

**Snack bars**

One of two types of snack bar will be provided to you during the "diet-supplementation" weeks of this study (Weeks 1-2, 4-5, 7-8). The intervention snack bar will contain different types of fiber and polyphenols. Fiber is a type of carbohydrate naturally found in plant foods (like fruits, vegetables, and grains), or made from sugars in those foods. The fiber used in this study will be oligofructose, inulin, galacto-oligosaccharides, and resistant starch type 2. These fibers are food for our gut bacteria, and are thought to have health benefits. Polyphenols are nutrients found in plant foods and can also feed our gut bacteria. Polyphenols help give fruits and vegetables their color, such as the blue in blueberries, and have many health benefits. The polyphenols used in this study will be from cocoa, green tea, cranberry, and blueberry. The second snack bar used in this study will be a placebo snack bar. A placebo is a non-active substance, like a sugar pill. The placebo snack bar used in this study will look and taste like the fiber and polyphenol bar, but it will contain no, or only very low amounts, of those nutrients. You will receive both types of bars at different times during the study, but you will not be told which bar you are receiving.

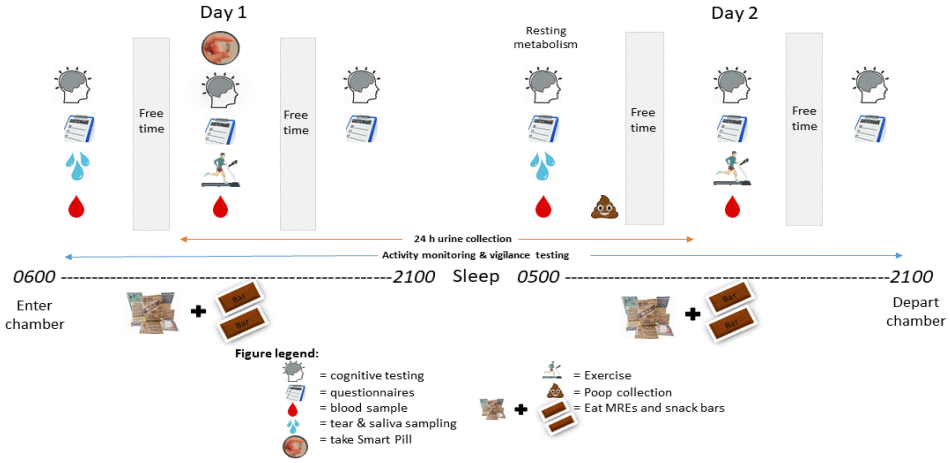
**Altitude chamber testing (Figure 1)**

The altitude chamber is located in the basement of USARIEM. It has three compartments; a bedroom, a bathroom with a shower, and a third room for exercise and other activities. During chamber testing, at least one study staff member will always be with you, and the chamber will be monitored continuously by "Chamber Chiefs." Up to 3 other study participants may be in the chamber with you as well.

At the end of each diet-supplementation phase, the altitude chamber will be set to one of two conditions. These conditions will approximate the environment at low or high altitude. We will not tell you which condition you are being exposed to. However, by the end of the study, you will have experienced both conditions. During both conditions, the chamber will be maintained under normal temperature and humidity. For the high altitude condition, the chamber will be set to simulate conditions at Pike's Peak in Colorado which is about 4300 m above sea level. For reference the peak of Mount Washington in New Hampshire is about 2000 m, Denver, CO is about 1600 m, and Santa Fe, NM is 2130 m.

The day *before* you enter the chamber we will give you water to drink so that you are hydrated when entering the altitude chamber. We will also give you a sterile urine cup so that we can collect a urine sample from you the morning that you enter the altitude chamber. Once you are in the chamber, all activities will be monitored by study staff (except for restroom activities). When not participating in testing, you will be allowed to participate in activities like reading and playing games, but will not be allowed to sleep or exercise except during designated times.

**Figure 1.** Example altitude chamber testing schedule. Times are approximate and may shift.*




*While COVID-19 risk reduction procedures are in place, tear fluid collection will not occur

## Post-study experiments

The poop samples collected from you will be made available for additional experiments to researchers at CCDC-Soldier Center and the University of Reading. These researchers will conduct experiments related to gut bacteria metabolism of nutrients, and interactions between gut bacteria and harmful bacteria. These experiments will be conducted using a machine that simulates the human intestine. Some of these experiments may not be directly related to the aims of this study. By consenting to participate in this study you are consenting to allow your poop samples to be used in future research that may not be directly related to the aims of this study.

## Additional activities for COVID-19 risk reduction

While COVID-19 risk reduction procedures are in place, we will ask you to participate in the following activities:

- **COVID-19 Screening:** At the beginning of each study visit, you will be asked if you are experiencing any COVID-19 related symptoms (for example, fever, cough, etc) and if you have been in contact with anyone diagnosed with COVID-19 within the past 14 days.

- **Temperature checks:** You will have your temperature taken before participating in certain study activities. If your temperature is >100°F you will not be allowed to participate in study activities on that day. Rather, you will be referred for medical screening. These activities include:
    - Exercise testing during Weeks 0 and 1
    - Resting metabolism during Weeks 0 and 1
    - Altitude chamber testing (Weeks 2, 5 and 8)

- **COVID-19 testing:** You will be tested for COVID-19 before each stay in the altitude chamber. As of June 2020, commonly used tests include a nasal or throat swab in which a long swab (similar to a Q-tip) is inserted into the nose or throat to collect a sample from the space located in the upper part of your throat and behind your nose. Other forms of testing include a saliva sample where you would spit into a tube. However, this method is currently less common. If you test positive for COVID-19 you will not participate in any study activities until you have recovered, and will be referred for medical screening.

**HOW LONG WILL I BE IN THE STUDY?**

If you agree to participate you will be in the study for about 10 weeks, and participate in about 173 total hours of study activities.

**WHAT PRECAUTIONS DO I NEED TO TAKE?**

- If female, you must not participate in the study if pregnant or breastfeeding.
- You must not exercise strenuously during the 24 hour period prior to living in the altitude chamber.
- You should sleep for 7-10 hours every night for portions of the study.
- You must not smoke or otherwise consume nicotine for certain portions of the study as instructed. Likewise, you must not drink alcohol and should avoid caffeine for portions of the study as instructed.
- You should not use medications like aspirin, ibuprofen or Aleve, or antihistamines, during the study.
- You should not take any diet supplements or eat any foods containing live bacteria (like yogurt) during the study.
- You must not donate blood within 8 weeks of participating in the study or during the study.
- For the time that the ingestible SmartPill is in your system you should not have a magnetic resonance imaging (MRI) test. A wristband notifying medical personnel of this will be placed around your wrist while the pill is inside of your body.
- You should not participate in the study if any of the following applies to you:
    - You are not willing to adhere to the instructions and procedures described above.
    - You have any injuries (like muscle sprains, broken bones) that make it difficult for you to exercise.

- You do not regularly exercise 3 or more days each week, or, if military, you did not pass your most recent combat/physical fitness test.
- You do not poop at least every other day.
- You do not have supervisor approval if active duty military or a federal civilian employee.
- You have medical issues such as heart disease, diabetes, or kidney disease.
- You have medical issues affecting your ability to swallow or your gastrointestinal tract such as narrowing of the esophagus, blockages anywhere in your intestines, and gastrointestinal diseases.
- You have a history of having a packed food ball that was unable to exit the stomach
- You have a sleeping disorder.
- You have any electronic medical devices implanted inside your body, or use a portable electronic medical device.
- You have ever experienced severe, life-threatening illness when travelling to high altitude.
- You have anemia or sickle cell anemia/trait.
- You have had gastrointestinal surgery.
- You have used oral antibiotics or had a colonoscopy in the past 3 months.
- You have alcoholism or another substance abuse disorder.
- You are allergic to skin adhesives.
- You follow a vegetarian or vegan diet.
- You regularly use medications that impact your pooping habits such as laxatives, stool softeners, or anti-diarrheal medications.

**HOW MANY PEOPLE WILL BE IN THE STUDY?**

Fifteen people will complete this study.

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

| Source | Risk | How we will minimize |
|---|---|---|
| Altitude exposure | Acute mountain sickness (AMS) (signs and symptoms include: headache, dizziness, lightheadedness, nausea, fatigue, shortness of breath, loss of appetite, vomiting) | • AMS is likely in this study.<br>• Will have you lay down if light-headed or dizzy.<br>• If severe, we will remove you from altitude chamber. |
| | High altitude pulmonary edema (HAPE) and high altitude cerebral edema (HACE) | • These conditions are unlikely but range from mild discomfort to potentially lethal. You will be monitored by study staff for any signs/symptoms.<br>• Excluded from study if experienced previously.<br>• If you experience signs and symptoms, we will remove you from the altitude chamber immediately. |

| | | |
|---|---|---|
| | Ear pain or discomfort | Provide nasal spray, and/or instruct on an ear clearing technique. |
| | Swelling of arms, legs, and/or face | Very low risk condition that goes away when you exit the chamber. |
| | Poor sleep in the chamber | • Poor sleep while in the chamber is likely during this study and a common side effect of high altitude exposure.<br>• Sleep quality will return to normal once you leave the chamber. |
| | Pregnancy complications | Females will be required to have a negative urine pregnancy test the morning that each altitude chamber residence period begins. |
| | COVID-19 is a respiratory disease that could increase and/or worsen risks related to altitude exposure, but we do not currently how much of an increase in risk, if any, this is. | • COVID-19 testing prior to entering the chamber.<br>• Temperature and symptom screening prior to entering the altitude chamber.<br>• Close staff and medical supervision for any unexpected symptoms while in the altitude chamber.<br>• You will be removed from the altitude immediately if experiencing any unexpected or unexpectedly severe symptoms. |
| Exercise | Lightheadedness; muscle discomfort, fatigue, or soreness; muscle or skeletal strains, sprains; accidental injury. | • You will be monitored by study staff during exercise.<br>• Stop exercising if lightheaded.<br>• Exercise restriction the day prior to chamber testing and aerobic fitness testing. |
| | Cardiovascular risk | You will be screened by medical staff to ensure you are healthy and fit to participate. |
| Blood sample collection | Local discomfort, swelling or bruising; dizziness or fainting; nausea/vomiting; minor risk of infection. | • Only trained and credentialed technicians will draw your blood.<br>• Technicians will use sterile technique. |
| Gut leakiness test | Gas, cramping, diarrhea, bloating | • Doses used in this study are not likely to have side effects.<br>• You will be asked to report any side effects, and may be removed from study participation if severe. |
| SmartPill | Choking; aspiration; pill becoming lodging in esophagus or intestines (this has happened in less than 1% of people without intestinal issues) | • You will not be allowed to participate if you have conditions that make it hard for you to swallow large pills.<br>• Staff will monitor pill ingestion.<br>• You will wear a bracelet while the pill is inside your body so that medical personnel know that you cannot have an MRI |
| Tear fluid collection | Eye irritation | Only trained technicians will perform this procedure. |

| | | |
|---|---|---|
| Diet changes | Sudden changes to your diet can cause gas, cramping, bloating, constipation, or other abdominal discomfort. | If symptoms are severe we may try to modify your diet or may withdraw you from the study. |
| Snack bars | The fiber in the snack bars can cause gas, cramping, bloating, constipation, or other abdominal discomfort in some individuals. | • We will have you consume 50% of the full dose during the 1st week of each supplementation period to allow your body to adjust.<br>• The doses selected for testing often do not cause, or cause only minimal side effects. |
| Data collection activities | COVID-19 infection | • COVID-19 screening and testing, and temperature checks as described above.<br>• Staff will not participate in data collection if experiencing symptoms or if they have had recent, known contact with someone infected with COVID 19.<br>• Staff will wear appropriate PPE such as face masks and gloves during study activities, use hand sanitizer, and maintain social distancing whenever possible.<br>• Staff will have their temperatures checked prior to entering the altitude chamber and will not enter the chamber if > 100°F<br>• We will ask you to wear PPE (face masks gloves, etc) whenever possible and to wash your hands/use hand sanitizer often. We will also ask you to maintain social distancing whenever possible.<br>• Frequently touched surfaces/equipment will be cleaned and disinfected before and after use.<br>• We will minimize sharing of equipment among participants.<br>• You will be provided sanitary wipes/disinfectant and asked to occasionally wipe surfaces/equipment you touch while participating in study activities.<br>• When in the altitude chamber, you will be asked to stay on a bunk bed behind a plastic barrier (like a shower curtain) when not participating in study activities. |
| COVID-19 testing | As of June 2020, nose and throat swabs are the most common forms of testing. Risks are minor but may include gagging, discomfort, and nosebleeds. | • Tests will be administered by trained healthcare professionals.<br>• There is also a chance of testing negative when you are in fact infected with COVID-19. |

These treatments and procedures may cause risks to an embryo or fetus that are unknown at this time.

**WHAT ARE THE POSSIBLE BENEFITS FROM BEING IN THIS RESEARCH?**

There are no direct benefits to you for participating in this study. However, results from this study are expected to help combat ration developers design new foods for optimizing the performance of Warfighters operating in high altitude terrain and other stressful environments.

**WHAT IF ANY UNEXPECTED INFORMATION IS LEARNED ABOUT MY HEALTH?**

Any health problems identified during the screening process will be documented and a copy provided to you. You will be encouraged to make an appointment with your primary care provider for a full evaluation of the problem. If you have evidence of any physical, mental, and/or medical conditions that would make participating in this study relatively more hazardous, you will not be allowed to participate.

**WILL RESEARCH RESULTS BE SHARED WITH ME?**

Yes. We will be able to share results of your fitness test, resting metabolism measurements, and SmartPill measurements if you are interested.

**WHAT ARE MY OTHER OPTIONS IF I DO NOT PARTICIPATE IN THIS STUDY?**

The only alternative to participating in this research is to not participate.

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

If you do not live on the Natick Soldier Systems Center, you will be responsible for paying for your transportation to and from the center. You will not be reimbursed for any travel costs or other costs related to participation in this research.

**WILL I BE PAID TO TAKE PART IN THIS RESEARCH?**

Yes. Volunteers who are active duty military or government employees who are on duty during research participation will receive $50 for each successful blood draw, for a total of up to $600 by study completion. If you do not complete the study, you will be compensated for each blood draw you successfully completed. For active duty military personnel we will also submit paperwork to petition for hazard duty pay for any testing completed in the altitude chamber.

Civilian volunteers who are not government employees and off-duty federal government employees will be compensated up to $1300 for completing the study. If the study is not completed, compensation will be based on the study activities completed at the time participation ends. The following payment schedule will be used to prorate compensation: medical screening: $10; baseline testing: $25; week 1 $20; week 2, 5 and 8 (days 1-5): $15; weeks 2, 5 and 8 (in altitude chamber): $3.75/hr up to $150 for 40 hr; weeks 3, 4, 6, 7, and 9: $12. You will receive an additional $70 if you complete the entire study. You will also receive

$50 for each successful blood draw, for up to a total of $600 if you successfully complete all blood draws.

You will receive payment within approximately ten weeks of study completion. Your social security number (SSN) will be needed to process your payment, as required by law. This information will be carefully protected. 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 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.

If you are injured because of your participation in this research and you are not a DoD healthcare beneficiary, you are entitled to care for your injury at DoD 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 DoD hospital or clinic will provide care. If you obtain care for research-related injuries outside of an 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. If you believe you have sustained a research-related injury, please contact the Principal Investigator (PI). If you have any questions, please contact the PI (J. Philip Karl; 508-206-2318 (office); 617-823-8074 (cell); james.p.karl.civ@mail.mil).

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

All data and medical information obtained from you will be considered privileged and held in confidence. To protect your privacy, any of your research-related records, including biological samples (blood, urine, poop, saliva, tears), and answers to questionnaires and computer tests will be “coded” with an assigned research participant number that will not include your name or any other identifying information such as your social security number, address, date of birth, zip code, etc. This participant ID number will be used on all data collection sheets and computer records. The principal investigator and the project coordinator will keep the link between your participant number and your research records in a locked cabinet or in a password-protected computer file. The principal investigator and project coordinator are the only people who will be able to match your research participant number with any of your personal identifying information. The master key linking your ID number to your name will be destroyed when the study is closed.

All study samples will be stored using your subject identification number. Your biological samples (urine, blood, poop, saliva, tears) and data will be shared with researchers at the CCDC-Soldier Center; the WRAIR; and the University of Reading. Any shared data will be transferred using secure methods. Some of your data may also be analyzed using the SysBioCube platform which is a secured website used by the WRAIR. No personally identifiable information will be shared with CCDC-Soldier Center, WRAIR, or the University of Reading, and no personally identifiable information will be uploaded into the SysBioCube website. Any collected data and samples will be stored indefinitely using your subject identification number.

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 videos or audio-tape recordings of you will be used for educational purposes, your identity will be protected or disguised. All identifiable or recognizable information (e.g., names and faces) will be covered in any photographs unless you agree to sign a photo release form. If you do not sign a photo release form, any photographs taken of you will be destroyed.

Complete confidentiality cannot be promised to military participants because certain health information may be required to be reported to appropriate medical or command authorities. 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 responsible for review and oversight of human research
- DoD and other Federal offices charged with regulatory oversight of human research
- US Army Research Institute of Environmental Medicine, Office of Research Quality and Compliance

Identifiers might be removed and de-identified material may be used for future research without consent.

The U.S. Army Medical Research and Development Command (USAMRDC) keeps information about volunteers participating in USAMRDC-conducted research in a confidential “Volunteer Registry Database”. The information includes your name, address, social security number, the name of the study you participated in and the dates of your participation. This information helps the USAMRDC be able to inform volunteers if new risks or important information are found. The information will be stored at the USAMRDC for a minimum of 75 years.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This 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 Web site at any time.

**WHAT IF I DECIDE NOT TO PARTICIPATE IN THIS RESEARCH?**

It is your choice whether you want to participate in this research. You can choose not to be in the study now or stop taking part in this research at any time without any penalty or loss of benefits to which you are entitled. Deciding not to participate now or withdrawing at a later time does not harm, or in any way affect, your medical care or future relationships with USARIEM or CCDC-Soldier Center.

If you decide to withdraw, you will be compensated for the portion of the study you completed. The data and samples collected from you will be retained by study investigators and may be used when analyzing the results of this research. If you decide to withdraw from participation please tell the principal investigator or study coordinator.

**WHAT COULD END MY PARTICIPATION IN THE RESEARCH?**

The principal investigator may withdraw you from participating in this research if circumstances arise which warrant doing so. This includes if you are unwilling or unable to comply with study procedures (including diets/exercise prescriptions), if you become ill or injured, if you repeatedly and/or intentionally do not follow COVID-19 risk reductions procedures, or if it would not be in your best interest to continue the study. The principal investigator will make the decision and let you know if it is not possible for you to continue. Your taking part in the study may be stopped without your consent if it is determined by the principal investigator that remaining in the study might be dangerous or harmful to you.

**WHAT IF ANY NEW INFORMATION IS FOUND OUT?**

During the course of the research, the investigators will tell you, in person, 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.

**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 J. Philip Karl (the Principal Investigator); Office phone: 508-206-2318; Cell phone: 617-823-8074

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 Human Protections Director at (508) 206-2371 or by email to usarmy.natick.medcom-usariem.mbx.usariem-rqc-protocol@mail.mil.

---

**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