UNIVERSITY OF OREGON

Colorado-Oregon Altitude Study – Informed Consent

NCT: not yet assigned

June 17, 2022

UNIVERSITY OF OREGON

Consent for Research Participation

Title: **C**olorado **O**regon **A**ltitude **ST**udy (COAST)

Sponsor: Partnership for Clean Competition (PCC) and Special Operations Command (SOCOM) – U.S. Department of Defense (DOD)

Researcher(s): Andrew Lovering, University of Oregon

Researcher Contact Info: (541) 346-0831

lovering@uoregon.edu

You are being asked to participate in a research study funded by the Partnership for Clean Competition (PCC) and US Special Operations Command (USSOCOM). The box below highlights key information about this research for you to consider when making a decision whether or not to participate. Carefully consider this information and the more detailed information provided below the box. Please ask questions about any of the information you do not understand before you decide whether to participate.

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

Key Information for You to Consider

- **Voluntary Consent**. You are being asked to volunteer for a research study. It is up to you whether you choose to participate or not. There will be no penalty or loss of benefits to which you are otherwise entitled if you choose not to participate or discontinue participation.
- **Purpose**. The purpose of this research is to determine the effects of two different interventions, iron and erythropoietin (EPO), on acclimatization to altitude.
- **Duration.** It is expected that your participation will last approximately 31 days of active testing spread out over 2+ months. This time is split up into several baseline visits (6 total) in Eugene, OR, followed by 4 weeks of interventions (10 visits to the lab), 14 days living in Colorado (approximately10,000 ft) during the summer of 2022, and 1 additional day of testing upon returning to Eugene, OR. You will be required to co-habitate while in Colorado
- **Procedures and Activities.** You will be asked to perform various exercise tests at baseline and at altitude, including a VO_2max test, army physical fitness tests, a 5km run, and an uphill run carrying a 35-pound backpack. You will also perform cognitive function tests have blood drawn and perform various breathing tests at baseline and at altitude, the details of which are all described below. You will be required to follow all CDC guidelines for minimization of COVID19 infection and transmission during participation in this study including mask wearing, and you will be required to be fully vaccinated prior to enrollment in this study.
- **Risks.** Some of the foreseeable risks or discomforts of your participation include developing altitude related illnesses, complications associated with high intensity exercise, and inhalation of small amounts of carbon monoxide during breathing tests. All risks are discussed in detail below.
- **Benefits**. This research provides no direct benefit to your health.
- **Alternatives.** Participation is voluntary and the only alternative is to not participate.

Who is conducting this research?

The researcher Andrew Lovering from University of Oregon, is asking for your consent to this research.

Why is this research being done?

The purpose of the research is to determine whether iron or erythropoietin (EPO), the drug used for blood doping, will enhance acclimatization to altitude. Specifically, we want to determine whether drug supplementation affects exercise performance, development of altitude sickness, cognitive function, changes in oxygen carrying capacity, or changes in various molecules circulating in your blood at altitude. You are being asked to participate because you are an adult aged 18-40, you are a recreational athlete able to exercise at high intensities, and you have indicated that you do not meet our exclusion criteria. About 100 people will take part in this research.

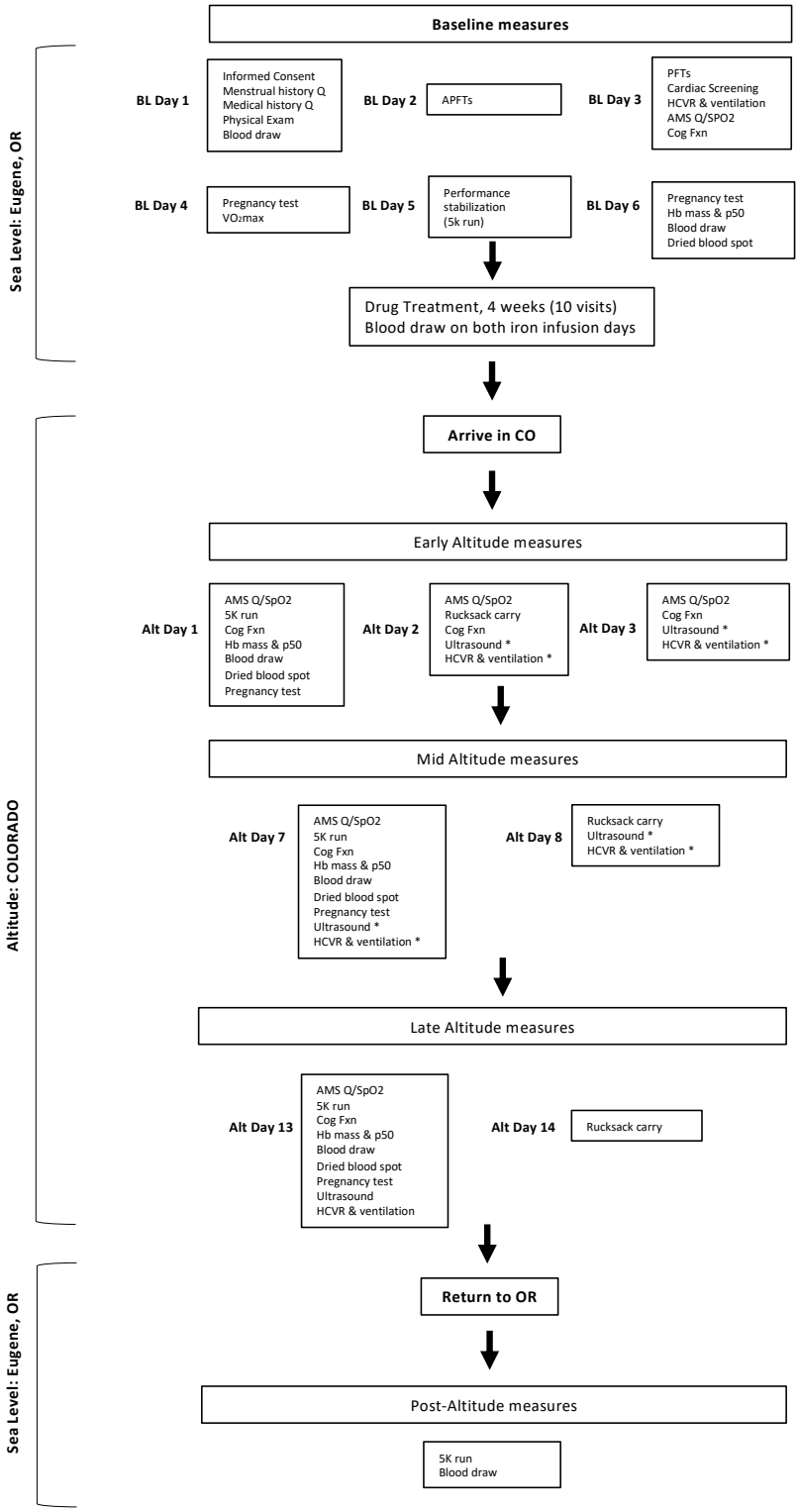
How long will I be in this research?

We expect that your participation will last approximately 31 days of active testing spread out over 2+ months. This time is split up into several baseline study days based on your availability and availability of research staff in Eugene, OR (6 days, see note below), 4 weeks of interventions in Eugene, OR (which involves 10 visits to the lab), 14 days in Colorado, and 1 additional day of testing upon returning to Eugene, OR. The 14 days in Colorado will occur in the summer of 2022, beginning in June/July. Baseline testing in Eugene, OR will occur throughout the spring/summer of 2022. The time commitment of your participation will depend on when you consent for this study. Your baseline visits could be completed within 1-2 weeks or over several months depending on your availability, and most of your visits are not required to occur within a certain time frame. Drug dosing will occur in the 4 weeks immediately before you travel to Colorado. You will not need to come to the lab every day for those 4 weeks but will report to the lab as required by your dosing schedule (between 1 and 3 days per week, total of 10 visits). The final 1 day of testing once you return to Eugene, OR will occur within 1 week of your return.

NOTE: Part 1 of the study will be performed over 6 days for baseline measurements to 1) screen subjects for inclusion in the study and 2) obtain baseline measurements with all studies conducted at the Cardiopulmonary Lab, Eugene, OR. However, you can choose to spread the baseline testing out over more than 6 days. Thus, you will spend approximately 6 hours getting screened.

What happens if I agree to participate in this research?

The following is a description of what you will be doing on each day of research. The table included at the end of this section will describe what you are required to do for each test. **Figure 1** below is also included to show a visual representation of what is described below. Any subject with childbearing potential will be required to take a pregnancy test whenever they are involved in VO2max testing or hemoglobin mass testing at baseline or at altitude, as the other testing days will not involve any activity that would otherwise affect the fetus. You will be given guidelines for participation in research activities to prevent COVID19 infection and transmission. These guidelines are driven by the CDC and may change during your participation.



* Indicates protocol that will be done on either day listed in early or mid altitude measures

Day 1 – Informed consent, medical History, blood draw: Cardiopulmonary Lab, Eugene, OR (approximately 60 min)

You will first complete this informed consent form. You will be given the option to undergo the informed consent process remotely, but you will not sign this form until you have arrived to the lab. Upon arriving to the lab, you will be asked to sign the informed consent and fill out a self-report health history questionnaire and menstrual cycle history questionnaire (biological women only) (approximately 30 min).
After completing paperwork, you will undergo a physical examination done by either a Nurse Practitioner or Physician Assistant – including a 25 mL blood draw – to verify iron status and basic health standards required for the study. The physical examination will be similar to what you would expect from a yearly physician's visit – non-invasive examination of lungs with a stethoscope, blood pressure measurements, etc. You will also be asked to sign a form to either give or deny the Lovering Lab permission to re-contact you after the end of the study. This may be for your participation in future studies or to collect more data for the current study after you deacclimatize. In addition, you will be asked to fill out a short survey to log exercise (the link will be emailed to you after consenting). This survey will be filled out once weekly for the duration that you are involved in the study, and on it you will provide details such as the types of activities you engaged in (running, lifting, walking, etc.), how long you engaged in those activities, and the relative intensity of those activities (approximately 30 minutes).

Day 2 – Army Physical Fitness Tests (APFTs), Cardiopulmonary Lab, Eugene, OR (approximately 60 min)

You will perform a modified version of the Army Physical Fitness Tests (APFTs) outdoors at the University of Oregon. The APFT will include 2 minutes of push-ups and sit-ups and a 5k run. Men (age 18-21) must be able to complete 42 push-ups in 2 minutes, 53 sit-ups in 2 minutes, and 5k run less than 24:42 (7:57 per mile pace). Women (age 18 – 21) must be able to complete 19 push-ups in 2 minutes, 53 sit-ups in 2 minutes, and 5k run less than 29:22 (9:27 per mile pace). If you come within 80% for each of the criteria, we may consider this passing. Total time approximately 1 hour. Below is a table with the 100% passing criteria for all 3 events for all age groups.

	Male APFT Standards				Female APFT Standards			
Age Group	**Push Up**	**Sit Up**	**Run (Pace)**	**Run Time (min)**	**Push Up**	**Sit Up**	**Run (Pace)**	**Run Time (min)**
18-21	42	53	7:57	24.42	19	53	9:27	29.22
22-26	40	50	8:18	25.47	17	50	9:48	30.27
27-31	39	45	8:30	26.25	17	45	10:15	31.51
32-36	36	42	8:51	27.29	15	42	10:51	33.43
37-40	34	38	9:09	28.26	13	38	11:21	35.15

Day 3 – Lung function. cardiac screening, blood draw, Acute Mountain Sickness (AMS) questionnaire with finger saturation and cognitive function testing: Cardiopulmonary Lab, Eugene, OR (approximately 125 min)

You will perform lung function testing (approximately 15 minutes), which involves breathing in and out of a mouthpiece. This testing involves two very similar tests, one called forced vital capacity and the other called slow vital capacity. You will be asked to breathe in and out of a mouthpiece as instructed by the researcher at various speeds and intensities. You will be instructed through the specific maneuvers by the researchers. You will also do cognitive function testing (~20 minutes), which involves 9 computerized tests to analyze reaction time, memory, and recall.

You will then have an intravenous catheter (IV) placed in your arm You will then undergo ultrasound screening to determine whether you have a patent foramen ovale (PFO), which is a hole in the heart that is present in approximately 35% of the population. During this test, you will breathe room air, and agitated saline (saline that has tiny opaque bubbles in it) will be injected into the IV. Those opaque bubbles can be visualized with an ultrasound machine and will tell us whether you have a PFO or not. Pulmonary artery pressure and cardiac output will also be measured using ultrasound (approximately 60 minutes).

You will complete two questionnaires that are used to measure acute mountain sickness (AMS), the Lake Louise Questionnaire (LLQ) and Environmental Symptoms Questionnaire (ESQ). For those questionnaires, you will be asked to rate how severely you are feeling a series of symptoms of AMS. Additionally, you will be instrumented with a pulse oximeter on either your finger or forehead to measure oxygen saturation (approximately 15 minutes).

Lastly, you will have resting ventilation (breathing) measured and your breathing response to high carbon dioxide (HCVR) measured (approximately 15 minutes). For the HCVR test, you will breathe in and out of a balloon or bag so that you inhale the carbon dioxide that you produce with each breath.

Day 4 – VO2max testing day, Cardiopulmonary Lab, Eugene, OR (approximately 30 min)

You will perform a VO_{2max} test (approximately 30 minutes). This test involves cycling at increasing intensities until you reach exhaustion. Additionally, resting, exercise, and post-exercise heart rate and systemic blood pressure will be measured. If you have child bearing potential you will be required to take a pregnancy test on this day.

You will arrive at the Cardiopulmonary lab and will be given a telemetric core temperature pill to take 5-10 hours before arriving for **Day 5** testing.

To take the core temperature pills, please swallow with a glass of water or other beverage. There are no restrictions for fluid or food consumption after you have ingested the pill. Please do not chew the telemetric pill. If you do not take the pill the night prior to exercise testing, you will have to take the temperature pill as a suppository the morning of testing. To insert the pill as a suppository, you will be instructed to insert the pill past the first digit of your finger. You will be given lubricant and a glove to help insert the pill as a suppository. Research staff can give you more additional information about the insertion process if you have more questions. These directions apply to every time you take the core temperature pill.

Day 5 – Performance Stabilization, Eugene, OR (occurs approximately 30 days before departure for Colorado)

You may be asked to come in for an additional day of testing to repeat the 5K run described above and in the table below. Only the top 80 subjects (and 20 alternates) with the most similar physical characteristics will repeat the 5k run. The reason for this is to make sure the different intervention groups are as similar as possible in their baseline fitness (approximately 30 min).

Day 6 – hemoglobin mass, Eugene, OR (occurs approximately 30 days before departure for Colorado)
You will perform hemoglobin mass (Hb mass) and p50 measures (approximately 60 minutes) to determine the oxygen carrying capacity of your blood. This measurement involves breathing carbon monoxide as well as additional blood draws. In total, approximately 76 mL of blood will be drawn, which is equivalent to approximately 5 tablespoons. Some of this blood will be to verify you do not have sickle cell trait or disease, (5 mL). The rest of the blood will be used to measure various biomarkers (60 mL), hemoglobin mass (Hb mass) and p50 (10 mL), which is the partial pressure of oxygen when your blood is 50% saturated. Dried Blood Spot samples will be taken utilizing a dried blood spot sampling device that requires a small prick on your arm for a very small blood sample (0.8mL). If you have child bearing potential you will be required to take a pregnancy test on this day.

Any abnormal findings revealed during the screening process will be shared with you and your physician upon request. We will encourage you to follow up with your physician if we find anything outside of the range or normal.

Drug Interventions

You will be randomly assigned into one of three intervention groups: iron, erythropoietin (EPO), or a placebo. You will not know which intervention you will receive. EPO will involve a needle injection just below the skin (similar to how you receive most shots at a doctor's office). Iron will involve an intravenous infusion over 2-5 minutes on two separate days. After the iron infusion, you will remain in the lab for 15 minutes to ensure you do not have an allergic reaction or adverse reaction. If you are randomly assigned to the placebo group, you will receive an injection of saline below the skin as the placebo for EPO and an intravenous infusion of saline as the placebo for iron.

For the 4 weeks immediately prior to the scheduled departure date, you will arrive at the Cardiopulmonary Lab as required by your dosing schedule (below) to be dosed with your assigned drug. Those assigned to the iron group will receive 2 infusions, one 4 weeks prior to departure and one within a week of departure. Those in the EPO group will receive injections 3x weekly for 3 weeks. The potential lasting effects of EPO should be back to baseline levels with 7 days of returning from high altitude so professional athletic competitions should be avoided until after that time. On the last day of the interventions, we will take an additional blood draw (60 mL) to determine if the treatments had any effect on various blood biomarkers, and 0.8mL for a dried blood spot measurement will be taken.

To ensure you do not know which group you are assigned, you will be required to arrive to the lab and receive a saline injection or infusion even if you are not scheduled to receive a drug. For example, if you are in the iron group, you will receive iron infusions twice (4 weeks and 1 week prior to departure) but still come to the lab to receive saline injections 3x weekly to provide the EPO placebo. In addition, if you are in the EPO or placebo group, you will receive intravenous saline infusions instead of iron. Despite this having no risk for

an allergic reaction, you will be required to remain in the lab for 15 minutes post-infusion to ensure you do not know which group you are in.

The table below describes what days you are required to come to the lab and what treatment you might receive on those days.

	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
4 weeks until departure				Saline Iron Saline			
3 weeks until departure		Saline Saline EPO		Saline Saline EPO		Saline Saline EPO	
2 weeks until departure		Saline Saline EPO		Saline Saline EPO		Saline Saline EPO	
1 week until departure		Saline Saline EPO		Saline Iron EPO		Saline Saline EPO	**Departure**

Early altitude measures: days 1-3, Colorado

You will fly from Eugene, OR to Denver, CO and be driven from Denver to Leadville or Breckenridge, CO (approximately 10,000 ft) where you will be housed and fed for 2 weeks. Prior to leaving Eugene, research staff will meet you at the airport to give you a core temperature pill to ingest 5-10 hr prior to your 5k trial on day 1 in Colorado. If you do not ingest the temperature pill you will be asked to insert the core temperature pill as a suppository

Upon arrival, you will fill out AMS questionnaires and have saturation measured. After, you will run the 5k time trial, perform cognitive function tests and then will be taken to preview the course for the rucksack carry to be performed on day 2. Dried Blood Spot samples will be taken utilizing a dried blood spot sampling device that requires a small prick on your arm for a very small blood sample (0.8mL). In the evening, you will have an IV placed and venous blood drawn (60 mL), and then you will perform Hb mass & p50 measurements (10 mL blood draw). Lastly, you will fill out AMS questionnaires and have saturation measured before going to sleep. If you have child bearing potential you will be required to take a pregnancy test on this day.

On day 2, AMS scores will be taken and saturation measured (morning and night), and you will participate in the rucksack carry. The rucksack carry is a 3.1 mile uphill run starting at 10,627 feet and ending at 12,595 feet. You will be carrying a 35-pound backpack and asked to complete the course as fast as possible. You will also perform cognitive function tests.

On day 3, AMS scores will be taken and saturation measured (morning and night), and you will perform cognitive function tests.

You will perform breathing tests (resting ventilation and HCVR) and ultrasound measures from Screening Day 3 on either day 2 or 3 at high altitude.

Mid altitude measures: days 7-8, Colorado

On the night of day 6, you will be given a telemetric core temperature pill to take 5-10 hours prior to the 5k run in CO (or insert as a suppository the prior to testing).

On day 7, you will do a repeat of most of day 1. AMS scores will be taken and saturation measured (morning and night), and you will run a 5k time trial, perform cognitive function tests, perform Hb mass & p50 measurements, and have venous blood drawn. Dried blood spot samples will also be taken. Total blood drawn for this day of approximately 71 mL. If you have child bearing potential you will be required to take a pregnancy test on this day.

On day 8, you will participate in the rucksack carry.

You will also perform breathing tests from screening day 3 (resting ventilation and HCVR) and ultrasound measures on either day 7 or 8 at high altitude.

Late altitude measures: days 13-14, Colorado

On the night of day 12, you will be given a telemetric core temperature pill to take 5-10 hours prior to the 5k run in CO (or insert as a suppository the prior to testing).

On day 13, you will repeat day 7. AMS scores will be taken and saturation measured (morning and night), and you will run a 5k time, perform cognitive function tests, perform Hb mass & p50 measurements, have resting ventilation measured, and have venous blood drawn. Dried blood spot samples will also be taken. You will also have ultrasound measures made on your heart, and you will perform breathing tests from screening day 3 (resting ventilation and HCVR). Total blood drawn for this day of approximately 71 mL. If you have child bearing potential you will be required to take a pregnancy test on this day.

On the morning of day 14, you will participate in the rucksack carry. You will be driven back to Denver, CO where you will fly back to Eugene, OR.

Post-altitude measures

Within 1 week of returning to Eugene, OR, you will return to the Cardiopulmonary Lab (Eugene, OR) to repeat the 5k run and blood draw only. Tests will be performed within 3-5 days after returning. Total blood drawn for this day of approximately 60 mL.

Note: During the 14 days at altitude, you will be involved in data collection on days 1, 2, 3, 7, 8, 13 and 14. On all other days, you are allowed to recreate as desired and will not participate in any research activities, ensuring that you follow CDC guidelines for COVID-19 risk mitigation. You will be reminded of your responsibilities prior to these 'off' days, such as eliminating alcohol consumption prior to upcoming study days.

The table below is meant to summarize the tests you will be performing:

Test	*Description of what you will do*
AMS questionnaires	Rate a list of AMS symptoms based on how severely you are experiencing them.
Cognitive function	Using a handheld computer, complete 9 tests meant to examine reaction time, memory, and recall.

HCVR (breathing response to carbon dioxide)	Breathe through an apparatus attached to a balloon/bag that allows you to rebreathe the carbon dioxide you produce each breath. Breathing will be easy at first, but expect to feel a strong urge to breathe by the end of the test.
APFTs	Perform 2 minutes of sit-ups, 2 minutes of push-ups, and run a 5k. Note: the 5k portion of this test will be performed on its own while at altitude, but no push-ups or sit-ups will be performed at altitude.
Rucksack carry	Run an uphill 3.1-mile trail as fast as possible starting from just over 10,000 feet in elevation and going up to just below 13,000 feet in elevation while carrying a 35-pound backpack.
Hemoglobin mass & p50	Breathe in carbon monoxide from a rebreathe apparatus and have blood samples drawn.
Lung function testing	Breathe in and out of a mouthpiece.
Ultrasound	Breathe room air and receive multiple injections of agitated saline (saline with tiny opaque bubbles) through an IV used to visualize a PFO.
IV & venous blood draw	Have an IV placed in your arm and blood taken from the IV.
VO_2max test	Cycle against increasing workloads until you reach exhaustion.

Please note: You will not be treated for AMS symptoms, but you will be treated for any other high altitude illness that may develop such as high altitude pulmonary edema or high altitude cerebral edema

We will tell you about any new information that may affect your willingness to continue participation in this research.

What happens to the information collected for this research?

Any information that is obtained in connection with this study and that can be identified with you will be de-identified using a random number coding system to protect you. With the exception of potentially sharing de-identified data with other investigators for research purposes, your de-identified data will remain confidential and will be disclosed only with your permission. Subject identities will be kept confidential and all coded subject information will be kept in locked file cabinets in Dr. Lovering's office. Research

Compliance Services and/or authorized representatives of the Food and Drug Administration (FDA) may need to review records of individual subjects. As a result, they may see your name in the decoder sheets, but they are bound by rules of confidentiality not to reveal your identity to others. The list of names, codes and decoding information will be kept after the study results have been published for at least 7 years, according to National Institutes for Health guidelines. Non-published data will be kept at least 10 years after collection.

How will my privacy and data confidentiality be protected?

We will take measures to protect your privacy, and we will take measures to protect the security of all your personal information. Despite taking steps to protect your privacy, we can never fully guarantee your privacy will be protected, nor may we fully guarantee confidentiality of all study information.

Your folder will be stored in locked file cabinets in Dr. Lovering's office. All other computer files associated with you will be identified only through your unique subject ID and stored on password protected lab computers. The de-identified data will be kept for at least 7 years after publication, per NIH guidelines. In the unlikely event the data are not published, they will be kept for at least 10 years after collection. This will ensure sufficient time for publication after data have been collected considering some trainees take up to 6 years to graduate, and often publication does not occur until many years after graduation.

You will be assigned an ID using a random number code system consisting of three to five letters describing the study (e.g., COAST) and a random, non-repeating number (1-300). This ID will be associated with your unique folder, which will contain all study documents and data collected including all associated forms (i.e. informed consent document).

The primary investigators will maintain a subject ID key capable of identifying subject IDs to subject names and contact information to provide us with the ability to identify subjects as additional questions or research findings arise. This ID key will be kept in a locked filing cabinet also within the offices of the primary investigators. No contact information will be stored with subject data. Department of Defense (DOD) representatives may have access to identifiable research records for regulatory oversight purposes.

De-identified data may potentially be shared with other investigators for research purposes, *without obtaining additional consent.* Some blood will be stored for later use; however, these samples will be unidentifiable, and only stored with an ID number that will indicate which intervention the sample had been exposed to.

If, upon your first visit you do not qualify for the study, any information will be immediately destroyed. Thus, if you do not consent to participate, the individually identifiable information will be destroyed.

What are the risks if I participate in this research?

The risks or discomforts of participating in this research include the following:

Confidentiality:

If data is lost or stolen, you could experience invasion of privacy. To minimize the potential invasion of privacy, we are not collecting social security numbers so that the potential economic impact is greatly minimized. All of our files will be kept in a locked filing cabinet to prevent theft and data will be de-identified.

Data acquired on computers will be password protected. As such, the ***probability*** of the adverse outcomes discussed above is low, and the ***severity*** is minimal.

Psychological:

For the echocardiography tests, female subjects will need to have no sports bra on to allow for imaging of the heart and the placement of small electrodes on the chest to record heart rate. To avoid any discomfort or embarrassment, you will be given a large, loose-fitting shirt (provided by researchers) to cover up. Male subjects will either go shirtless or be given a loose-fitting shirt. As such, the ***probability*** of the adverse outcomes discussed above is low, and the ***severity*** is minimal.

Physiological:

Travel: You will be transported between Eugene and Leadville or Breckenridge by automobiles and airplanes. Travel by road or air, carries the risk of injury or death. According to the National Transportation Safety Board, there are 0.0003 fatal accidents for every 1,000,000 miles flown by US carriers. The National Highway Traffic Safety Administration reports a fatality rate of 1.13 per 100,000,000 miles driven on US roads. To minimize this risk, only commercial, US carriers will be used for air travel and all traffic laws will be strictly obeyed.

Pulmonary (Lung) Function Tests: Risks associated with pulmonary function testing include shortness of breath, cough, dizziness, and possible loss of consciousness. To minimize risks, the co-investigators will administer all pulmonary function tests and allow you to rest between measurements. Lung function testing performed in our lab is a routine assessment performed in pulmonary function labs all over the world according to American Thoracic Society and European Respiratory Society standards. You can stop the test at any time if you feel any of the above symptoms. The probability and severity of these risks is very low.

VO_{2MAX} testing*:* You will perform a VO2max test where you exercise to volitional exhaustion. Criteria for terminating a VO2max include achieving: 1) heart rate greater than 85% of age-predicted max (220-age), 2) a plateau in oxygen consumption and/or a respiratory exchange ratio greater than 1.15; all of these criteria are continuously monitored on our metabolic system and Nellcor pulse oximeter. This carries the rare risk of dizziness, confusion, nausea, fatigue, difficulty breathing, abnormal heart rhythms, stroke, heart attack, and sudden death. In subjects less than 35 years old, the risk of sudden death of all causes is estimated to be 1 in 133,000 for men (Van Camp et al MSSE 1995). In this study only 100 of 136 deaths with identifiable causes were caused by cardiac events, so this estimate of risk may overestimate incidence of cardiac events. The overall risk of sudden death caused by a heart problem for all ages and sexes is estimated to be 1 in 15,000 to 18,000. (*Source:* American College of Sports Medicine - ACSM). As such, the ***probability*** of the adverse reactions discussed above is low, and the ***severity*** is very low (e.g. dizziness) to very high (e.g. sudden death).

Additional exercise tests (APFTs, 5k run, and rucksack carry): Hard exercise has inherent risks associated with it, including stroke and heart attack. These risks are very low in young, healthy individuals (less than 0.00006%). You may also feel dizzy, lightheaded, or unusually winded. These symptoms can be worse during exercise at altitude. If you feel faint or feel like you can't get enough oxygen, you will be instructed to tell study personnel as soon as possible. You may experience muscle injury and stiffness following exercise. Proper warm-up and cool-down procedures will minimize the chances of this occurring.

Risks associated with core temperature pill: The risks of using the temperature pills include mechanical injury to the mucus membranes if adequate care is not used. Risks of the temperature pill will be minimized by explaining the procedures to the volunteers. Additionally, ample lubricant (suppository) or water (oral) will be provided to the volunteer. Volunteers with history of obstructive diseases of the gastrointestinal tract including diverticulosis, diverticulitis, inflammatory bowel disease, peptic ulcer disease, Crohn's disease, ulcerative colitis, or previous GI surgery will not use a telemetric pill.

Intravenous (IV) catheter: Risks associated with placement of an IV include pain and/or bleeding during placement, vasovagal syncope, hematoma (pooling of blood under the skin), infection, and vessel blockage. The placement of the IV may cause some discomfort with rare bleeding or bruising at the puncture site. It also carries the risk of infection. To mitigate risks associated with vasovagal syncope, you will be safely positioned upright and sitting in an IV chair, and you will be continually monitored by Dr. Lovering and colleagues, all of whom are trained to place IVs. As such, the ***probability*** of the adverse reactions discussed above is low, and the ***severity*** is minimal.

Blood Removal: Risks associated with the removal of blood include an aversion to seeing blood that could result in nausea, vasovagal syncope, increased stress, and/or feeling faint. To mitigate these potential risks, you are continually monitored by Andrew Lovering PhD and colleagues. In addition, you are safely and comfortably positioned on either a gurney or IV chair. In this way, the potential risk of vasovagal syncope (i.e., fainting) is mitigated.

A total of ~435-465 mL of blood will be drawn throughout the study. The range up to 465ml is included in case extra samples are required for screening metabolic panels due to abnormalities in findings or compromised samples. Of that volume, 25mL will be drawn baseline day 1 as part of the physical examination. In total, ~162 mL will be drawn prior to departure to Colorado for metabolic panels, biomarker analysis, dried blood spots, Hb mass, and p50. An additional ~213 mL will be drawn during the 2 weeks at high altitude (max volume of ~71mL per day), and ~60 mL will be drawn as part of post-altitude testing. 1 pint of blood, the normal volume of blood donated on a given day, is ~473mL. Throughout the entire study, we will be taking less than that, and the maximum volume for a given day does not exceed ~76 mL. As such, the ***probability*** of the adverse reactions discussed above is low, and the ***severity*** is minimal.

The following table is meant to breakdown the volume of venous blood that will be drawn on a given day, as well as what it will be used for:

	Informed consent	Baseline 6	Post Treatment	Altitude 1	Altitude 7	Altitude 13	Post-altitude
Screening panels	25 mL	5mL	None	None	None	None	None
Biomarkers	None	60 mL	60 mL	60 mL	60 mL	60 mL	60 mL
Hb Mass & p50	None	10 mL	None	10 mL	10 mL	10 mL	None
Dried blood spot	None	0.08 mL	0.08 mL	0.08 mL	0.08 mL	0.08 mL	None

Saline Contrast Echocardiography: The PI has been using saline contrast echocardiography since 2003 to detect blood flow through intracardiac and intrapulmonary shunts. Risks: transient dizziness associated with agitated sterile saline injection in patients with cardiac shunting. With respect to exercise, the Principal

Investigator has greater than 10 years of experience using TTSCE in a research setting. In 4 years (2003-2007) at the University of Wisconsin Madison, approximately 60 human (male and female) subjects (including 8 subjects with a patent foramen ovale) were tested without a single adverse event related to TTSCE. Additionally, research done at the University of Oregon between 2008 and 2016 has involved greater than 100 subjects using TTSCE at rest and during exercise without incident related to the TTSCE. We will use agitated sterile saline without preservatives. Furthermore, we will use a minimal volume (3-5 mL) of sterile saline. Dr. Lovering and colleagues will perform saline contrast injections, while trained ultrasonographers will perform echocardiography. Mixed saline (saltwater), either alone or with 5% sugar in water **has been used to help see the ultrasound pictures (echocardiogram) for over thirty years**. Saline contrast bubble injections are routinely used to screen for the presence of a patent foramen ovale in the clinic. The American Society of Echocardiography Guidelines (2014) state that "…life threatening reactions are rare (less than 1 in 10,000)" when using contrast injections (including bubbles with protein shells) and The European Association of Echocardiography (2009) has stated that "… the evidence shows that contrast echocardiography is very safe in clinical practice." And this includes using stabilized bubbles with protein shells and we only use non-stabilized saline contrast bubbles in our lab. We only use a small amount of air mixed with saline, thus the ***probability*** of any ***severe*** adverse reaction is very low. Given the evidence presented above, the ***probability*** of the adverse reactions discussed above is low. Although the ***severity*** of arterial gas emboli is high, given the amount of air used and the short life span of intravascular bubbles of this size, the likelihood of the constellation of unfortunate events required for a serious adverse reaction to occur is very small.

Hb mass measurement: Risks associated with CO determination of blood volume include exposure to carbon monoxide. Most non-smoking city dwellers have 1.5-2.0% CO in their blood and the duplicate tests will increase it to approximately 15%. The level most commonly associated with symptoms is greater than 15%, with no symptoms reported at 10% or lower. Minor symptoms are present when CO levels rise to 30%. These symptoms may include: confusion, headache, fatigue, nausea, shortness of breath, dizziness, cough, and cherry-colored lips. To protect against an excessive increase in CO we will only test you if your baseline CO level is 2% or less. Further, if your post-CO rises to 20% or higher we will initiate oxygen therapy. This will have you breathe 100% oxygen, which reduces the CO half-life from 5 hours to 80 minutes and is the approved therapy used in a clinical setting to treat CO poisoning. We will then repeat oxygen therapy until it is below 8%. In the unlikely event that your CO bound to hemoglobin is excessive and does not appear to be responding to O_2 therapy we will call appropriate police dispatch, depending on the location of the incident (Eugene, OR or Colorado). This method has been in use in research in a wide variety of populations to measure Hb mass including elite athletes (male and female), untrained individuals (male and female), adolescents (11-15 year old boys and girls), elderly subjects, and pregnant women with no ill effects reported. The use of CO as a marker for measuring blood volume has been in use for over 100 years without notable complications. You will be verbally reminded of the symptoms associated with increased carbon monoxide levels prior to your participation in the CO uptake test and will be asked to notify researchers if you are experiencing any of the side effects of carbon monoxide during or after the test.

Altitude associated risks: Staying at high altitude causes systemic hypoxia (low oxygen). This decreased oxygenation can lead to several things depending on how high you go, how fast you go there, and how well adjusted to altitude you are. The consequences can range from mild to severe.

The most common symptoms of altitude exposure are feeling lightheaded, dizzy, or short of breath during exercise. We expect up to 40% of people to feel one of these things while at altitude. A smaller number of people will develop acute mountain sickness (AMS). AMS is a name for the combination of headache and

lack of appetite, difficulty sleeping, upset stomach, throwing up, or feeling weak. These symptoms are usually temporary and manageable. They typically do not threaten peoples' health.

Traveling from baseline to altitude can, in rare occasions, lead to more serious conditions. Two of these include high altitude pulmonary edema (HAPE) and high altitude cerebral edema (HACE). Both of these conditions are potentially fatal if left untreated. HAPE is a serious disorder that sometimes occurs with a fast change in altitude (going up). It occurs in less than 1% of people going from baseline to altitudes used in this study. The 5k run will be at 9,075 feet above baseline. The uphill hike will start at 10,627 feet and go to 12,595 feet. Subjects will sleep at 10,570 feet. This sleeping altitude is not expected to produce HAPE. HAPE symptoms are treatable if found early. They usually show up 2-3 days after ascent to altitude. HAPE may be preceded by AMS. The inability to breathe while resting is the hallmark of HAPE. You may also have a bad cough, blue lips, fever, or fast heart beat. You will be instructed to immediately notify study personnel if you feel out of breath at rest. Suspected HAPE cases will be treated by a doctor familiar with the condition.

The other serious complication of altitude is HACE. HACE is very rare. The possibility of seeing HACE is extremely low. In our previous studies involving greater than 150 volunteers at these altitudes in Colorado, HAPE and HACE have never been seen. As with HAPE, it is treatable if recognized early. Loss of coordination and mental confusion are the major symptoms of HACE. HACE victims typically show AMS or HAPE first. If you start to behave irrationally or appear very uncoordinated, you will be treated by a doctor immediately.

To protect you during their stay in Colorado, we will monitor you in several ways. Your oxygen levels will be monitored with a standard finger oximetry (Nellcor N-200). You will also fill out a questionnaire designed to quantify the level of AMS you are experiencing, if any. Furthermore, you will be monitored for other signs that you are proceeding down a path that may threaten your health. These include severe AMS symptoms: a severe headache that does not go away, uncontrolled vomiting, extreme dizziness, or excessive weakness. Other signs include: blue fingernails, trouble breathing while resting, unsteady walk, extreme paleness, or incoherent or bizarre behavior. Medical personnel will treat these symptoms immediately. Oxygen and transportation back to Denver will be available at all times. In the event of a life-threatening emergency, we will call 911. Although we do not expect most of these symptoms to develop, we cannot rule out the possibility. It is important to note that the combined experience of the research team amounts to over a century of doing this type of study with no severe adverse events in that time.

During the rucksack carry, there is cell phone service throughout the hike. You will be accompanied by the research team who will be ahead of and behind you. Research assistants are setup along the trail with radios (walkie talkies) to contact the teams ahead of and behind you with updates on your status. The Colorado group has completed over 300 runs with research subjects in these exact same conditions with no medical adverse events to date. Any of the vehicles we will be driving can transport you to the Frisco medical center within 15-20 minutes. St. Vincent Health is 1.4 miles from Colorado Mountain College so the response time in event of an emergency is ~5-10 minutes. A physician will be on the course with a vehicle, with supplemental medical oxygen, and a full field first aid kit at all times you are on the course.

There are also risks of being in the mountains. The most significant environmental risks include lightning strikes, traumatic injury from falls in rough mountain terrain, and sunburn from the higher UV-light exposure. These risks will be minimized by requiring you to remain in the vehicle or indoors during electrical storms; by prohibiting you from any rock climbing activity, and by making you aware of the sunburn risk and supplying them with sunscreen. Finally, the investigators have more than three decades of experience

conducting field research and dealing with these challenges, including recent experience with an identical protocol in identical mountain setting with nearly identical testing procedures and with no serious unanticipated outcomes.

Hypercapnia during rebreathing tests: Risks associated with breathing hypercapnia (high carbon dioxide) at rest include feeling light-headed, headache, fatigue, dizziness, shortness of breath. You will be monitored with a peripheral estimate of arterial oxygen saturation using a forehead monitor to ensure you are well oxygenated and we will continuously monitor inspired and expired oxygen and carbon dioxide levels. As such, the ***probability*** of the adverse reactions discussed above is moderate, and the ***severity*** is minimal.

Risks associated with drug treatments: Some of the known risks associated with EPO are joint/ muscle/bone pain, fever, cough, rash, nausea, vomitting, soreness of mouth, itching, headache, redness and pain in the skin where EPO shots are given, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence. Some of the known risks associated with iron are pain and swelling at the site of injection. In order to minimize these risks, all precautions and warning labels will be followed, and dosing volumes will be strictly adhered to. You will be excluded from the study for any health problems that may negatively affect their reaction to these drugs or have a history of anemia, venous thrombosis or plans for professional competition during or after participation.

Risks for subjects who are pregnant: Potential risks to subjects who are pregnant (beyond the risks outlined above for the general population) include exercising beyond than what is recommended by their doctor (see 'VO_{2max} testing' and 'additional exercise testing' above) and potential unknown risks to the child bearer or fetus from carbon monoxide inhalation (see 'Hb mass measurement' above). None of the additional risks described above are greater in those who are pregnant. Due to the increased risk of exercise testing and Hb mass measurements, if you have childbearing potential you will be required to take a pregnancy test on a day that involves maximal exercise testing (VO2max) and Hb mass testing while at baseline and in Colorado, and if such a test comes back positive, you will be immediately excluded from the study. Therefore, there is no added risk to the child bearer or the fetus from any of the above-mentioned protocols, as they will not undergo those procedures. As such, the probability of an adverse reaction is zero, and the severity of an adverse reaction is zero.

COVID-19 related risks: Due to the SARS-Cov2 pandemic, there is the added risk of COVID-19 infection for you and staff in this study. To mitigate this risk, **you and all research personnel will be vaccinated before the initiation of any study.** To further mitigate this risk, you and all research staff, regardless of CDC guidelines, will wear masks when participating in research activities. This does not include research activities in which you have to remove your mask to participate (i.e. during Hb mass when you are expected to breathe on a mouthpiece); however, during those activities in which you will not wear a mask, the research personnel will be masked. Additionally, per standard protocol, all mouthpieces will be disinfected with Cidex and all surfaces wiped with disinfecting wipes between participants. Researchers will wear appropriate PPE, including masks, lab coats or scrubs, safety glasses, and gloves. Additionally, proper social distancing can be done with most protocols described above, i.e. maintaining 6 feet between you and researchers. When possible, testing will be performed outdoors to maximize social distancing (i.e. during 5km and uphill rucksack tests). While the severity of COVID-19 infection has the potential to be severe, the measures described to mitigate this risk make the likelihood of an event low. You will also be reminded during the consent process and throughout the study that failure to comply with these precautions will result in your removal from the study. You will be cohabitating in Colorado, so to minimize COVID outbreaks you will be

assigned to research groups of 4-5 so that if one of you develops COVID, we can minimize transmission within our other groups. You will wear masks, wash hands frequently and will have hand sanitizer in each room while cohabitating.

COVID-19 exposure plan: Prior to departure to Colorado, you will self-monitor symptoms and be told to not come in to the lab if you experience any symptoms of COVID and get tested if recommended by current CDC and University of Oregon guidelines. While in Colorado, research team members will screen all participants daily for symptoms and signs of COVID. If you report symptoms that suggest you have COVID, transportation will be provided to the closest COVID testing center. You or your insurance company will be responsible for costs related to the COVID test, if there are costs incurred. If your COVID test is positive prior to or while in Colorado, you will be withdrawn from the study and be treated by local medical personnel according to CDC guidelines. You or your insurance company will be responsible for any costs related to medical care for COVID. Research team members will check on you closely and will work to arrange safe transportation back to Oregon when the medical personnel tell us it is safe for you to travel.

Compensation for an injury or assistance with medical bills resulting from your participation, including contracting COVID, in the course of this research is not available from the University of Oregon or Research Logistics LLC. If you get sick or injured as part of your participation in this study, you or your insurance provider will be charged for the cost of the care.

COVID Vaccine: Given the availability of vaccines for all adults and the added risk of co-habitating for this research project, being fully vaccinated will be a requirement to participate in the study. Any subject that refuses to get vaccinated will be excluded from further study. Currently, all researchers are fully vaccinated. Your vaccination card will be scanned, and identifiable data (name, birthday, etc.) will be blacked out prior to photocopied vaccine card being added to your folder. You will be considered fully vaccinated to the extent that is recommended by the CDC and University of Oregon (for example, if a booster shot is recommended and available, you and researchers must receive it).

COVID Compliance protocol

Compliance to CDC guidelines for minimizing risk of exposure to COVID-19 must be adhered to for the duration of the study. In order to hold you accountable, you will be emailed a Qualtrics survey to check 'yes, I have been following appropriate COVID protocols', or 'no, I have not been following appropriate COVID protocols' in your reminder email prior to every lab visit in Oregon. You will also be required to fill this survey out starting weekly 30 days prior to departure to Colorado. You will be required to fill out this survey daily while in Colorado reporting that you are following CDC guidelines, and you will have the opportunity to report pod mates who are not following guidelines. Additionally, each week you will be updated on any changes to CDC guidelines which will be included as part of the survey. You may feel uncomfortable reporting your pod mates for not following COVID-19 procedures. To mitigate this risk, all reporting will be done via an anonymous online survey.

COVID transportation protocol

When you depart for Colorado, you will be given a "covid-19 travel bag" which will include one 4 oz bottle of hand sanitizer (minimum 60% alcohol), 3 KN95 masks, and several alcohol wipes. We will ask you to do the following while traveling:

- Before walking into the airport: put KN95 mask on, this will stay on the entire duration of airplane travel

- When seated on airplane use alcohol wipes to disinfect all touch surfaces by the seat including the lap tray, buckle, arm rests, overhead light/air controls, and if in window seat, the window screen pull. Then, use hand sanitizer to clean hands.
- After exiting the airport in Colorado trash the first KN95 mask and replace with a fresh one, this mask will be used for the duration of the bus ride to Leadville or Breckenridge, CO. Use hand sanitizer.
- When seated in the bus, use alcohol wipes to disinfect all touch surfaces by the seat. Use hand sanitizer.
- Upon arrival to Leadville or Breckenridge, CO, trash the bus KN95 and replace with a fresh mask. Use hand sanitizer.
- You will be given a new "covid-19 travel bag" when you depart from Colorado so that your travel back may be as safe as possible. You will be expected to follow the same protocol for traveling to Eugene as you did while traveling to Colorado.

What are the benefits of participating in this research?

This study will not make your health better. This study is only being done to gather information. Some of the benefits that may be expected include a better understanding of the processes of altitude acclimatization.

What are my responsibilities if I choose to participate in this research?

If you take part in this research, you will be responsible for:

- Following all instructions given by the research teams.
- Drinking adequate water (2 liters of water per day) at altitude.
- Limiting caffeine intake to 2 6oz cups of coffee per day on active study days.
- Eliminating alcohol and drug consumption prior to any study days.
- Eliminating exercise not required by the research team on the day before exercise tests.
- Disclosing new medical information to the research team, including new medications or supplements and possible COVID-19 exposures.
- Following proper COVID-19 guidelines as outlined by local, state, and federal governments.
- Obtaining a COVID-19 vaccine if not already vaccinated.
- Ensuring you have health insurance, and that your health insurance has out of state/out of network coverage.

Failure to follow the above responsibilities will result in elimination from the study and prorated payment.

What if I want to stop participating in this research?

Taking part in this research study is your decision. Your participation in this study is voluntary. You do not have to take part in this study, but if you do, you can stop at any time. You have the right to choose not to participate in any study activity or completely withdraw from continued participation at any point in this study without penalty or loss of benefits to which you are otherwise entitled. Your decision whether or not to participate will not affect your relationship with the researchers or the University of Oregon, University of Colorado, or Northern Arizona University. You do not waive any liability rights for personal injury by signing this form. If you choose to stop participating in the study partway through, your compensation will be prorated based on the time already committed.

If you choose to stop participating in the study, any data collected so far will remain part of the study database and may not be removed. In addition, collected blood specimens may be stored and used for biomarker analyses in the future without additional consent.

Will it cost me money to take part in this research?

There is no cost to you associated with the research. Should you choose to participate, your airfare to and from Colorado will be paid for. Lodging and food while in Leadville or Breckenridge will be paid for.

What if I am injured because of participating in this research?

If you are injured or get sick because of being in this research, call the researchers immediately. All forms of medical diagnosis and treatment whether routine or experimental, involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the researchers will assist you in obtaining appropriate medical treatment. The investigators may stop you from taking part in this study at any time if it is in your best interest, if you do not follow the study rules, or if the study is stopped. If you are physically injured because of the project, you and your insurance company will have to pay your doctor bills. If you do not have out of state coverage, there is the risk of these doctor bills being extremely high. If you are a UO student or employee and are covered by a UO medical plan, that plan might have terms that apply to your injury.

If you experience harm because of the project, you can ask the State of Oregon to pay you. If you have been harmed, there are two University representatives you need to contact. Here are their addresses and phone numbers:

General Counsel/ Office of the President 1226 University of Oregon Eugene, OR 97403-1226 (541) 346-3082	**Research Compliance Services** 5237 University of Oregon Eugene, OR 97403-5237 (541) 346-2510

A law called the Oregon Tort Claims Act may limit the amount of money you can receive from the State of Oregon if you are harmed.

Will I be paid for participating in this research?

In return for the time and effort, you will be compensated for the study visits completed as follows:

- Baseline Screening: $75
- Performance Stabilization: $25
- Colorado Week 1: $400
- Colorado Week 2: $400
- Post-study visit(s): $100

All expenses (airfare, lodging and food) will be paid for your trip to Colorado. You will receive 2 checks if you complete this study. One will be in the amount of $600 from Research Logistics, LLC. A second check will be in the amount of $400 from University of Oregon. You will be mailed both checks approximately 2 weeks after completion of the study. If you do not complete all study procedures or violate the study rules (such as

drinking excess caffeine or violating CDC guidelines for lessening COVID-19 exposure risks), payment will be prorated based on the above.

Please be aware, compensation for participation in research may be considered taxable income. The University requires tracking for compensation that is paid to you; this may include your name and contact information. Because you will receive $600 or more in a calendar year, you will be asked to provide additional (e.g. Social Security Number) information for tax reporting purposes. This information is stored confidentially and separate from research data.

Who can answer my questions about this research?

If you have questions, concerns, or have experienced a research related injury, contact the research team at:

University of Oregon: Andrew Lovering, PhD, and Colleagues
(541) 346-0831
lovering@uoregon.edu

An Institutional Review Board ("IRB") is overseeing this research. An IRB is a group of people who perform independent review of research studies to ensure the rights and welfare of participants are protected. UO Research Compliance Services is the office that supports the IRB. If you have questions about your rights or wish to speak with someone other than the research team, you may contact:

Research Compliance Services
5237 University of Oregon
Eugene, OR 97403-5237
(541) 346-2510

STATEMENT OF CONSENT

I have had the opportunity to read and consider the information in this form. I have asked any questions necessary to make a decision about my participation. I understand that I can ask additional questions throughout my participation. I understand that DOD representatives may have access to identifiable research records for regulatory oversight purposes.

I understand that by signing below, I volunteer to participate in this research. I understand that I am not waiving any legal rights. I have been provided with a copy of this consent form. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

I consent to participate in this study.

Name of Adult Participant	Signature of Adult Participant	Date

Researcher Signature (to be completed at time of informed consent)

I have explained the research to the participant and answered all of his/her questions. I believe that he/she understands the information described in this consent form and freely consents to participate.

Name of Research Team Member	Signature of Research Team Member	Date

TELEMETRIC PILL CONSENT

I meet the inclusion criteria and consent to participate in the core temperature arm of this study. I agree to take the telemetric pill at sea level for performance stabilization and on days 1, 7, and 13 at altitude.

Name of Adult Participant	Signature of Adult Participant	Date

Name of Research Team Member	Signature of Research Team Member	Date