Informed Consent Document
Florida Institute for Human and Machine Cognition (IHMC)

Title of Project: Ketone Body Administration Impact on Work Capacity and Physiologic Reserve at Altitude

All researchers who conduct studies using human Participants are bound by professional ethical standards for the conduct of such research. These standards are mirrored in the rights that are guaranteed to research participants by federal law (NIH regulation 45-CFR-46). The purpose of this document is to inform you of these rights and obtain your assurance that you have been made aware of your rights.

1). Before deciding whether to participate, it is your right to be presented with an overview of the project that explains the purposes of the research.

The general goal of this research is to test whether a ketone ester drink helps offset some of the negative physical performance effects associated with hypoxia (breathing less oxygen than the amount available at sea level).

2). Before deciding whether to participate, it is your right to be presented with a description of the general research approach and methodology.

This study will consist of 3 sessions, each performed on separate days. The first day consists of study briefing and informed consent, questionnaires, and collection of baseline data including a maximal exercise test on a stationary cycle, submaximal exercise, and a body composition assessment. The remaining 2 study days (separated by a few days) will involve submaximal exercise tests on the same stationary cycle. For all 3 sessions you will consume a provided meal in the morning and for sessions 2 and 3 you will also consume a study drink. The type of drink you consume will be predetermined in randomized fashion.

Briefing/Consent/Baseline (Day 1):
After you provide informed consent, you will complete some questionnaires, consume a small meal, complete a body composition scan, and then undergo a maximal exercise test and submaximal exercise on a cycle ergometer.

Submaximal Exercise Tests with Study Drinks (Days 2 and 3):
During these two sessions you will consume the same light meal, complete some questionnaires, consume one of the two study drinks (ketone drink or placebo), undergo 3 blood measurements (finger sticks), and undergo a resting period and submaximal exercise while breathing through a mask that mimics being in the mountains at about 15,000 feet above sea level by providing you with a lower amount of oxygen than you normally breathe near sea level. During these testing sessions, we will monitor your heart rate, blood pressure, metabolic activity, and your perceptions of effort.

If at any time you believe that you are having a medical emergency during or following your participation, please immediately notify the research staff and call 911. If you experience side effects that you believe might be related to your participation, or have any complaints or concerns about the research, please notify the study team at: task7@ihmc.org; Institute for Human and Machine Cognition, 40 S. Alcaniz Street, Pensacola, FL 32502.

3). Before deciding to participate, it is your right to understand any risks or stresses that may be involved in your participation.

In this study, you might experience physical strain or discomfort while undergoing the hypoxic exposure. It is important to understand the potential risks, likelihood of risk, and severity of risks of participating in this study for the following reasons:

Hypoxia: Hypoxia is a state of oxygen deficiency that can impair function. It is associated with high altitude exposure when the breathing air does not contain sufficient oxygen or is not delivered with sufficient positive pressure. Symptoms of hypoxia may include air hunger, numbness, tingling, headache, fatigue, nausea, hot and cold flashes, euphoria, visual changes and hyperventilation (breathing too fast and deep). Hypoxia is a risk factor in the current study, but also the objective. It is unlikely that you will experience significant adverse symptoms due to hypoxia exposure. Likelihood: High; Severity: Low.

Finger Blood Collection: Capillary blood samples will be captured using a lancet to poke your finger. This may cause pain, discomfort, or bruising. Additionally, while very unlikely, anytime blood is drawn, there remains a risk for disease transmission. Likelihood: Low; Severity: Medium.

Confidentiality: There is always a risk of confidentiality loss in research. Your demographic and personal identifiable information (PII) will be documented for the study and there is an unlikely risk that the information collected could be breached. Likelihood: Low; Severity: Low.

Nausea or Gastrointestinal Distress: There is a chance that ketone or placebo supplementation may cause discomfort via nausea or gastrointestinal irritation. Likelihood: Low; Severity: Medium.

COVID19 or other Infectious Disease: Participants and researchers are at risk of disease transmission during direct interactions. Likelihood: Low; Severity: Low.

Maximal and Submaximal Exercise: Maximal and submaximal exercise may cause pain and discomfort. The absolute risk of an exercise-related cardiovascular event varies with age and comorbidities but is extremely low in healthy active individuals. Likelihood: Low; Severity: High.

Low Dose Radiation Exposure: Participants will be exposed to low dose x-rays during a single body composition scan. The radiation exposure is less than that experienced during commercial air travel from New York to California. Likelihood: Low; Severity: Low.

These risks will be minimized in the following ways:

Hypoxia: Hypoxia exposure will occur through a breathing mask providing lower than normal sea level oxygen levels. You can remove the mask at any time to return to breathing room air. Thus, nearly instantaneous breathing of room air can begin in the case of untoward events. The mask will be removed by researchers in the following situations: you report limiting symptoms, you complete the session time, your oxygen saturation levels fall below 50% at the finger, you become incoherent or incapable of performing the task, or you request to terminate the session. To help prevent excessive hypoxia exposure, your oxygen saturation and heart rate will be monitored by a researcher throughout each session. There are no significant risks associated with the physiological monitoring devices using in this study. No tissue damage is expected. A medical research monitor, who is independent of the study team and who has extensive experience in handling hypoxic symptoms, can also be consulted as needed.

Finger Blood Collection: A lancet needle will be used to standardize the finger stick. The lancets and metabolite meters used are commercially available and routinely used by individuals with diabetes and during performance assessments. Researchers will clean your skin (alcohol swab) prior to using the lancet to retrieve drops of blood. The research team has conducted hundreds of capillary finger sticks without adverse event.

Confidentiality: You will be assigned an alphanumeric code called a Participant ID (PID) that will be used in place of PII. From that point forward all data collected will be stored by PID only. Codes will be assigned at random. The electronic key linking the alphanumeric PID to PII will remain protected; accessible only by authorized IHMC research personnel. Electronic files containing study data collected will list you only by alphanumeric code. Such files will be stored on password-protected computers/tablets/servers/clouds; accessible only by approved research personnel. Upon completion of data collection, analyses, final report, and manuscript development, the stored key linking PID and PII will be destroyed.

Nausea or Gastrointestinal Distress: The ketone drink being tested has been administered at rest and during exercise by the researchers in several studies. While minor nausea and gastrointestinal discomfort may occur, severe nausea and GI distress are not common. The ketone drink is considered "generally recognized as safe" (GRAS) by the US Food and Drug Administration and has been studied for safety (Clarke et al. 2012, Stubbs et al. 2017, Stubbs et al. 2019, Soto-Mota et al. 2019).

COVID-19 or other Infectious Disease: IHMC research personnel are trained in best practices to reduce risk of disease transmission among researchers and participants. These precautions may include symptoms pre-screening, exposure status, and personal protective equipment (PPE), as appropriate.

Maximal and Submaximal Exercise: To mitigate risks associated with maximal and submaximal exercise, you will be properly screened, and your heart rate and blood pressure will be monitored during the exercise tests as needed to assess cardiac function. IHMC has highly trained research personnel who have conducted numerous maximal and submaximal exercise tests. Research personnel are CPR certified and are trained on emergency procedures. If you feel undue discomfort or pain during testing, you are free to stop at any time.

At least two researchers will be with you at all times to help protect your safety. In the event that an injury or adverse event occurs that does not require immediate medical attention, a trained research staff member on site (who is competent in risk mitigation and participant safety) will take appropriate steps for your safety. A medical monitor with extensive experience in handling hypoxia symptoms will not be on site during study procedures but will be available via phone communication.

Research personnel will communicate any injuries or adverse events to the medical monitor to obtain medical guidance, and to the PI of the study. In the event of a medical emergency 911 will be called.

If you incur an injury or medical condition as a result of your participation in this study, your personal medical insurance will be responsible for any costs associated with treatment.

4). Before deciding to participate, it is your right to understand any alternative experiences or courses of action.

This study will evaluate nutritional supplements that aim specifically to influence the ketone body level in the blood and improve physical endurance, metabolic efficiency, and oxygen consumption. There are

other commercial products available through nutrition and health food stores that also affect ketone body level. In addition, eating a ketogenic (high fat, low protein, very low carbohydrate) diet provides another option for increasing ketone levels in the body. We ask that you refrain from using these alternatives before and during your participation in this study.

5). Before deciding to participate, it is your right to understand that the data are to be kept confidential.

All data will be coded and kept confidential under lock and key in the office of the study PI for 5 years following study completion. Specifically, the data we collect from you will be archived using identification codes so that your name will not be associated with data or statements.

Your name will not be identified in any analyses, reports, or write-ups of the results. You may only be identified in terms of their general characteristics (e.g., age, education level, experience, etc.).

We will use descriptive statistical methods to analyze participant data. Data analyses, groupings, or summaries of this type will bear no annotations that identify the participants.

6). Your participation is voluntary. Your participation will have no influence on anything that falls outside of this research context. A decision to not participate will involve no penalty or loss of benefits to which you are otherwise entitled, and you may discontinue participation at any time and for any reason.

7). Before deciding to participate, it is your right to understand that *DURING* the research itself you can continue to exercise your rights.

In research of this kind, there are no "right" or "wrong" answers. There is no such thing as "incorrect" behavior. You are encouraged to simply be yourself and exercise your knowledge and skills as appropriate to the research tasks that you will be asked to perform.

You can ask any questions you may have, at any time.

It is your right to withdraw/discontinue your participation at any time. You may do so for any reason, and you are not required to disclose your reason. Should you choose to discontinue your participation, this will not in any way affect or influence anything outside of this research context.

It is your right to be given a copy of this Informed Consent Document to keep.

Your performance of the research tasks will not in any way affect or influence anything that falls outside of this research context.

8). Who to contact for answers to pertinent questions about the research and participants' rights, and who to contact in case of a research-related injury.

Research related questions, including research related injury:

Marcas Bamman, PhD, Principal Investigator
Florida Institute for Human and Machine Cognition
40 S. Alcaniz St., Pensacola, FL 32502
task7@ihmc.org

Participants' rights related questions:

Anil Raj, MD
Chair, IHMC Institutional Review Board
Florida Institute for Human and Machine Cognition
40 S. Alcaniz St., Pensacola, FL 32502
(850) 202-4456
araj@ihmc.org

Dr. Raj also serves as the medical monitor for this study. You may contact him for questions related to your study experience.

If you are injured because of your participation in this protocol, you should contact your healthcare provider. No other funds are available to compensate you for injury or costs of additional treatment. By signing this consent form and taking part in this study, you are not giving up any legal rights you may have. In the event of medical emergencies, please contact 911.

9). Before deciding to participate, it is your right to understand why your participation may be terminated by researcher(s) without regard to subject consent.

The following events would constitute exclusion/termination from study participation without your consent:

- Event occurs following consent which changes your eligibility or safety.
- Research staff become aware of information following consent which indicates you are not eligible to participate.

10). Before deciding to participate, it is your right to understand that *AFTER* the research itself you can continue to exercise your rights.

Once your participation is over, it is your right to request that all data you have provided be discarded. You may do so for any reason, and you are not required to disclose your reason. This will not in any way affect or influence anything that falls outside of this research context.

Federal or Department of Defense (DoD) representatives, including but not limited to the DoD Office of Human Research Oversight, will have access to review identifiable research data collected from this study.

11). Before deciding to participate, it is your right to understand the way in which you will be compensated.

You will not receive monetary compensation for participating in this study.

You will not accrue any additional costs from participating in this study.

12). Before deciding to participate, it is your right to understand the sponsorship of this research.

This research is funded by the US Department of Defense (USDOD).

13). Before deciding to participate, it is your right to understand the interests of the researcher(s).

The Department of Defense is funding the company Health Via Modern Nutrition (HVMN) and IHMC to evaluate the effect of the ketone ester drink on exercise responses during hypoxia. IHMC research staff salaries are partially supported by DoD funding.

14). Optional Permission for audiovisual records.

If you have any questions now, please feel free to ask them.

The researchers may want to use a short portion of video or audio recordings made during your participation for illustrative reasons in presentations of this work in the classroom or at professional meetings and publications. Please initial one of the following options:

_____ The researchers may not use any audiovisual records of my participation in this study.

_____ My face and voice may appear, but not my name.

_____ My name, face and voice may appear

Your signature below indicates you have read and understood this Informed Consent Document. You will receive a copy of the signed and dated consent document.

Participant's Signature	
Date	
Researcher's Signature	
Date	

Researcher's full name, address, and contact information	Name: _____ Florida Institute for Human and Machine Cognition 40 S. Alcaniz Street Pensacola, FL 32502 850-202-4462 task7@ihmc.org