

**H00014860 Acetazolamide on High-Altitude Pulmonary Edema**  
**Version 2 – 02/10/2018**  
**INVESTIGATOR STUDY PLAN**

NCT03490916

**APPROVED 3/14/18**

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**. TITLE**

A Prospective, Double-blind, Randomized, Placebo-controlled Trial of Acetazolamide on Subclinical High-Altitude Pulmonary Edema (HAPE) Detected by Lung Ultrasonography

**2. EXTERNAL IRB REVIEW HISTORY\***

N/A

**3. PRIOR APPROVALS:**

Wilderness Medicine Society (WMS) – Study grant pending

Nepal Health Research Council (NHRC) – pending. NHRC generally requires outside institutional IRB approval before they will give final approval. Once final approval is obtained, it will be uploaded.

**4. OBJECTIVES\***

The overall goal of this study is to detect preclinical signs of HAPE by lung ultrasonography and evaluate the effectiveness of acetazolamide at decreasing pulmonary edema by using ultrasound.

**5. BACKGROUND\***

See attached WMS grant proposal page 2-3

**6. INCLUSION AND EXCLUSION CRITERIA\***

Inclusion criteria: 1.) At least 18 years of age; 2.) Able to consent; 3.) English speaking; 4.) Trekking directly to Everest Base Camp

Exclusion criteria: 1.) Age less than 18 years; 2.) Non-English speaking; 3.) Pregnant; 4.) Already had a diagnosis of acute mountain sickness, high-altitude cerebral edema, or HAPE 5.) Had been on a high-altitude trek 2 weeks prior to this study 6.) Has taken acetazolamide 1 week prior to start of trek 7.) Has a sulfa allergy 8.) Has any type of acute or chronic pulmonary conditions

**7. STUDY-WIDE NUMBER OF SUBJECTS\***

N/A

**8. STUDY-WIDE RECRUITMENT METHODS\***

N/A

**9. STUDY TIMELINES\***

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We will recruit subjects from the 2018 Wilderness Medical Society (WMS) Everest Base Camp Trek. The WMS 2018 Everest Base Camp Trek is a trekking trip from Lukla, Nepal (2840m) to Everest Base Camp (5400m) in Spring 2018. The duration of the trek is approximately 3 weeks. The duration of enrollment will be approximately 1-2 days during preparation part of the trip in Kathmandu, Nepal at the beginning of the trek. The estimated date for completion of primary analyses will be December 2018.

WMS Everest Base Camp Trek Itinerary

March 25	Arrival in Kathmandu, transfer to hotel (1310m)
March 26	Sightseeing in Kathmandu and preparation day **Enrollment day**
March 27	Fly to Lukla (2840m), trek to Phakding (2610m)
March 28	Trek to Namche (3440m) **Data Collection 1**
March 29	Namche and slow walk to Kunde Hospital/Kumjung
March 30	Extra day in Namche and visit Namche Bazar (3440m)
March 31	Trek to Tengboche (3860m)
April 1	Trek to Pheriche (4270m) **Data Collection 2**
April 2	Pheriche / hike Nakarsang Hill (5200m)
April 3	Pheriche
April 4	Lobuche (4910m) **Data Collection 3**
April 5	Gorakshep (5140m)
April 6	Hike to Kalapathar (5550m) / Everest Base Camp (5364m)
April 7	Everest Base Camp (5364m) **Data Collection 4 & 5**
April 8	Pheriche
April 9	Khumjung (3760m)
April 10	Manjo (2835m)
April 11	Lukla(2840m)
April 12	Fly back to Kathmandu
April 13	Kathmandu farewell dinner **Data Collection 6**
April 14	Final departure to home

\* May change slightly depending on weather, conditions, etc.

**10. STUDY ENDPOINTS\***

Primary outcome measures: 1.) Pulmonary edema detected in lung ultrasound exams before and after taking acetazolamide.

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Secondary outcome measures: 2.) Time to completion of ultrasound exams

### 11. PROCEDURES INVOLVED\*

After informed consent has been obtained, subjects will be randomized to receive either of the study medications medication: 250mg of acetazolamide or a placebo pill. Investigator will be blinded as to which arm of the study the patient is enrolled. Medications will be obtained from the UMass Pharmacy in individual blister packs. We will ensure that acetazolamide and the chosen placebo pill look similar. Any identifying information on the blister pack will be obscured by a black marking pen, if necessary. Medications will then be inserted into small opaque envelopes and marked with only a number. Numbers will be assigned to medications by use of the random number generator function (=RANDBETWEEN(1,30\*)) (\*The final number will depend on the total number of subjects) in Excel with the top half of the list being assigned Acetazolamide and the bottom half placebo pill. The list will then be sorted in numerical order in Excel. When a subject enrolls, a number will be assigned in order. Blinding of the numbers and assigned medications as well as the assembly of the envelopes will be done prior to leaving UMass by PI's faculty advisor who will not be involved in medication administration.

At each of the time points noted in #9, lung ultrasound exams will be done at bedside in a private location to measure the total ultrasound lung comets (an ultrasound finding for pulmonary edema) for a "comet score." One (1) single dose of 250mg acetazolamide or placebo will be given at Everest Base Camp (Data Collection #4) and a comet score will be measured again 12 hours after acetazolamide or placebo is given. Previous studies have shown that comet scores increase with altitude and given that Everest Base Camp is the highest altitude the subjects will be residing at, it is believed that we will find the biggest decrease in comet score if acetazolamide is given at this point. The subject's heart rate and oxygen saturation will also be collected via a pulse oximeter.

Acetazolamide is a drug that has been approved by FDA for use of prevention of acute mountain sickness. Acetazolamide is not approved for prevention of HAPE and is investigational for this study. While it is FDA-approved to be used to treat acute mountain sickness, many previous studies and current guidelines have recommended the use of acetazolamide prevention HAPE. The investigation does not involve a route or dosage level that significantly increases the risks associated with the use of the drug product. This investigation does not involve a patient population that would significantly increase the risks associated with the use of the study drug.

Bedside ultrasound is a non-invasive modality of imaging that is routinely used and employed in clinical practice. It does not involve input of radiation into the subjects or an invasion of the subject's privacy. Subjects thoraces will be scanned in a private setting in lodging. Both left and right thoraces will be scanned. 28 total ultrasound images will be recorded during each session (16 on the right and 12 on the left). Please see attached WMS grant proposal page 2-5 for details of the methods of ultrasound scanning. Each session is expected to take approximately 5 minutes.

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Ultrasound images will be stored on password-protected encrypted Android tablets that are used to gather ultrasound images. There is limited internet connectivity in this remote region of Nepal and upload of ultrasound images is not always feasible in the field.

No medical record review will be done.

No use of a Humanitarian Use Device will be employed.

#### **12. DATA AND SPECIMEN BANKING\***

N/A

#### **13. Data Analysis and Management\***

Previous studies in lung ultrasonography suggest that a minimum of 14 subjects will be needed to provide 80% power to detect a statistically significant difference in ultrasound lung comets. Between 20-30 total subjects are expected.

For data analysis, Fisher's exact test will be used to compare categorical variables. Continuous variables will be analyzed with paired Student's t-test. Linear regression models will be used to assess correlations between ultrasound lung comets and vital signs. In all cases p values < 0.05 will be considered significant. Data will be reported as mean +/- SD

#### **14. PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS\***

The study is designed to give only one (1) dose of medication. If there is any adverse reaction to acetazolamide, subject will be evaluated by PI or WMS trip leaders, who are trained in emergency medicine and wilderness medicine. A decision will be made to whether or not to continue the study for the subject. Common side effects include:

- headache
- diarrhea
- feeling or being sick, loss of appetite, thirst, or a metallic taste in the mouth
- lightheadedness
- looking flushed
- a need to pass urine more often than normal
- tiredness or irritability
- feeling over-excited
- a tingling or numbness in the fingers or toes, or coldness in the extremities.

Symptomatic treatments will be provided as needed. Subject will be given a choice whether or not to continue with the study, which will only involve ultrasound scanning, for the rest of the trek.

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In the case that ultrasound imaging picks up findings that could indicate that subject is at risk of developing high-altitude pulmonary edema, in addition to any subject displaying signs of severe altitude illness, they will be treated and evacuated as determined necessary by the WMS medical providers present. The 2018 WMS trip leaders are Emergency Physicians who are trained in wilderness medicine and have substantial experience diagnosing and treating altitude illness and arranging evacuations in Nepal. Participants requiring evacuation will be accompanied by a guide. In the event that an individual cannot descend on foot, helicopter evacuation is possible up to Everest Base Camp. All WMS trip participants are required to carry evidence of Evacuation and Medicine Travel insurance that covers high altitude. Participation in this research project will not dictate or change treatment or evacuation in any way.

This study involves no more than minimal risk to subjects, and therefore will not utilize a DSMB.

#### **15. WITHDRAWAL OF SUBJECTS WITHOUT THEIR CONSENT\***

Subjects may be withdrawn from the study if they become exceedingly ill or injured, unconscious, or require evacuation. In this case, the data already collected will remain in the study, but subjects will not complete future data points.

#### **16. RISKS TO SUBJECTS\***

This study poses minimal risks to participants, mainly the brief exposure of skin to ultrasound gel and probe during image acquisition. Image acquisition happens while indoor inside lodging and duration should not exceed 5 minutes per session. The study is 3 weeks and participants can withdraw at any time if they feel uncomfortable with continuing the study.

There is also a risk of breach of confidentiality. Though we will not be recording patient names or medical record numbers, we will be tracking subject demographics tied to a unique identifier along with recorded ultrasound images.

Acetazolamide is a drug that has been approved by FDA for use of prevention of acute mountain sickness. Potential side effects including but not limited to lightheadedness, paresthesia's of fingers and toes, change in urination frequency, and change in taste of beverages. These side effects are more common in the persistent use of acetazolamide and are unlikely when taking only one single dose. If subject has an allergic reaction to acetazolamide, subject will be evaluated and treated for allergic treatment, if necessary. Treatment includes but not limited to diphenhydramine, prednisone, and intramuscular epinephrine

While being at high altitude can cause physical discomfort and psychological stress as well as the risk of developing high altitude illness, this is a risk that participants have chosen to undertake prior to being enrolled in the study. Participating in this study does not add to this risk and may even help subjects be more aware of any altitude illness symptoms that are developing.

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**17. POTENTIAL DIRECT BENEFITS TO SUBJECTS\***

N/A

**18. VULNERABLE POPULATIONS\***

N/A

**19. MULTI-SITE RESEARCH\***

This study is being conducted simultaneously with study #H00014129. While the studies are on the same subjects, the studies are expected to minimally impact each other. The main potential effect the studies could have on each other is the time that will take for each to be completed at a time point, however neither data collection is expected to take more than 20 minutes per subject. The pulmonary ultrasound measurements of study #H00014860 are short duration and not expected to impact cognitive function or the ability of subjects to answer questions on the concussion software. The concussion apps in this study do not require physical exertion except minimal effort during a short time standing and balancing and are not expected to impact pulmonary edema or the ultrasound measurements.

Study #H00014860 involves a single dose of acetazolamide or placebo at Everest Base Camp. The concussion app data for this time point will be collected before the medication is given and therefore should not be impacted. An additional data point 12 hours later at Everest Base Camp will be added to assess any effect of the medication on the concussion app data for study #H00014129. While this study's main goal is not to assess the effect of acetazolamide on the cognitive functions measured by the concussion apps, it may add useful information both for this study and for study #H00014860. The half-life of immediate release acetazolamide is 5-6 hours and is expected to have been excreted prior to the next time point six days later after descent.

**20. COMMUNITY-BASED PARTICIPATORY RESEARCH\***

N/A

**21. SHARING OF RESEARCH RESULTS WITH SUBJECTS\***

Since ultrasound images will not be definitely reviewed until after the trek is completed, we will not be sharing the results with the subjects during the trek. However, as we consent each subject, they will be asked whether or not if they want the final results to be shared with them after the study is completed. If the subject chooses to have results to be shared with them, they will be contacted via subject's preferred contact method after all the ultrasound images reviewed and results have been gathered. Research results will not be shared with anyone else.

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In the case that ultrasound imaging picks up findings that could potentially indicate that subject is at risk of developing high-altitude pulmonary edema, necessary steps will be taken as described in #14

#### **22. SETTING**

Altitude illness has the highest incidence at extreme altitudes, especially over 14,000 feet, which is limited in the U.S. to a handful of summits, making it difficult to study domestically. However, this altitude and higher is easily found in the Himalayan mountains. Nepal is a well-established site for altitude research.

Data collection will take place in rural Nepal in the Himalayan mountains along the usual approach route to the Mt. Everest basecamp. Image acquisition of the subjects will take place in the dining area of tea houses (local hostels with attached restaurants). The dining rooms are the only areas of the tea house that are heated and lit in the evening hours.

Dining rooms serve as points of congregation for the trip. Though they are public spaces, participant privacy will be accommodated by setting up a research station in a quiet room.

#### **23. RESOURCES AVAILABLE**

Principal Investigator: Design and oversee the project. Obtain funding and necessary approvals. Set up hand-held ultrasound tablets. Travel to Nepal and collect data. Acquire images. Publish results. PI is a residency-trained physician in emergency medicine, currently in completing emergency ultrasound fellowship with extensive experience in bedside ultrasonography. PI also has experience in backpacking and camping in remote environments as well as experience in international travel.

Faculty Advisor: Will accompany PI during the trek and oversee another research project. The faculty advisor has experience with conducting research in rural Nepal at the proposed site for multiple prior studies. The faculty advisor is fellowship-trained in wilderness medicine and has significant experience in backpacking and camping in remote environments, international travel including Nepal and Asia, required travel medications/vaccinations, and mountain trekking safety. The faculty advisor has knowledge of the culture, customs, and society in Nepal as well as some basic knowledge of the Nepali language. The faculty advisor also has significant experience ascending to high altitude, identifying and treating high altitude illnesses, and potential evacuation options should an emergency arise.

#### **24. LOCAL RECRUITMENT METHODS**

Subjects will be recruited from the Wilderness Medical Society 2018 Everest Experience Trek to Basecamp participants. This is an annual CME trip organized by the Wilderness Medical Society in which participants ascend from Kathmandu to Everest Base Camp and return. The CME trip



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usually has between 20-30 participants. We will aim to recruit all eligible subjects from this group.

We will contact trip participants by email with study after they register for the trip. This recruitment email has been included in this submission.

As the WMS Trip gives required CME presentations in English, all trip participants speak English. We will not enroll adults unable to consent, minors under age 18, pregnant women, prisoners, or non-English speaking subjects.

Subjects will not be compensated or paid to participate in the study.

**25. LOCAL NUMBER OF SUBJECTS**

See #24. All subjects will be recruited from the Wilderness Medical Society 2018 Everest Experience Trek to Basecamp participants with a goal of 20-30 participants depending on the size of the CME trip registrants (exact number not available until registration closes in early 2018.)

**26. CONFIDENTIALITY**

Data will be collected including patient's vital signs and will be recorded with ultrasound images and data collection sheet. This information will be obtained from the study subject via pulse oximetry. The medical record will not be accessed. Digital images of ultrasound exams will be recorded for later review as described. Ultrasound images are recorded and stored on the password-protected encrypted handheld Android tablets during the duration of the trek. These images will be transferred to a secure password-protected hard drive in the locked offices of the Division of Emergency Ultrasound once back in the United States. Access to these images will be limited to study personnel and the UMASS IRB.

No patient identifiers (e.g. name, medical record number) will be linked to this information. A unique subject ID will be used to track data and link to ultrasound images. Final results of image interpretation by expert reviewer will be stored in an Excel spreadsheet in the UMass servers.

Only study personnel and the UMASS IRB will have access to the data. All study paperwork including electronic database information will be maintained for 3 years following completion of the study.

In the case that subjects are suspected of having HAPE during the trek, subject's information may be shared with trek leaders. Subject information may be subjected to different or fewer confidentiality protections than exist under US regulations, because the research is being conducted internationally. It is possible, although unlikely, that information may be shared with trek leaders, other medical personnel, or otherwise subject to subpoena in cases of severe illness/injury or death.

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**27. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS**

Ultrasound exams will take place in a private room without the presence of others. Since it might require subject to expose their thoraces briefly, a bedsheet or similar barrier available in the lodging will be used to cover the subject during their exposure. We will not access any protected health information.

**28. COMPENSATION FOR RESEARCH-RELATED INJURY**

We anticipate that the research with ultrasonography and one dose of acetazolamide will pose minimal risk to subjects. We do not anticipate there will be any research-related injury. In the event of trip-related injury or illness, participants on the WMS CME trip will already be carrying personal travel insurance.

**29. ECONOMIC BURDEN TO SUBJECTS**

There is no cost to the subject to participate in the study.

**30. CONSENT PROCESS**

Once the final registration has closed for the WMS Trip, registrants will be given information about the study. If they choose to participate, they will review and sign the consent form at the hotel during the WMS Trip's time in Kathmandu. The PI will follow current guidelines for obtaining informed consent and answer any questions that subjects may have. We will not enroll any non-English speaking subjects.

Please see uploaded written consent form.

**31. PROCESS TO DOCUMENT CONSENT IN WRITING**

Subjects will review and be asked to sign the attached consent form. The PI will review and will follow [\*HRP-803 INVESTIGATOR GUIDANCE: Documentation of Informed Consent\*](#) prior to obtaining informed consent.

**32. DRUGS OR DEVICES**

The drug in this study is acetazolamide. It is IND exempt under 21 CFR §312.2(b). Acetazolamide is currently lawfully marketed in the United States. The investigation does not involve a route or dosage level that significantly increases the risks associated with the use of the drug product. Acetazolamide is not approved for prevention of HAPE and is investigational for this study. While it is FDA-approved to be used to treat acute mountain sickness, many previous studies and current guidelines have recommended the use of acetazolamide for prevention of HAPE. This investigation does not involve a patient population that would significantly increase the risks associated with the use of the study drug.

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Handheld ultrasound has been used clinically for diagnosis of medical conditions. Pulmonary edema is a condition that is commonly diagnosed through ultrasound in clinical settings in hospitals. The protocol of this study simply looks for signs of pulmonary edema at a high-altitude setting. The protocol of this study does not deviate from traditional protocol to evaluate pulmonary edema, does not evaluate the safety or effectiveness of device, and is being used in accordance to use approved labeling.