

Hyperbaric Oxygen Therapy in Sickle Cell Pain Crisis (HAVOC)  
NCT03412045  
Protocol and Statistical Analysis Plan  
2025-03-12

**Biomedical Research  
SECTION I****1. Status:**

♦ New Submission

Revised electronic IRB Application; IRB#

Initial electronic submission of an existing expedited IRB approved protocol; IRB#

**2. Title of Protocol:**

(HAVOC) Hyperbaric Oxygen Therapy in Sickle Cell Pain Crisis

**3. Responsible Personnel:****A. Principal Investigator (PI):**

Cooper, Jeffrey Scott - Emergency Medicine - 402-552-2490 - jeffrey.cooper@unmc.edu -

alt #: 402-559-4000 - degree: MD - address: UT UNMC Midtown (Zip 1150) - phone: 2-2490

**B. Secondary Investigator (SI):**

Coffey, Shaila Kay - Emergency Medicine - 402-559-6802 - shaila.coffey@unmc.edu - alt #:

402-559-6802 - degree: MD - address: UT 3237 UNMC Midtown (Zip 1150) - phone: 9-6123

Telken, Wyatt Ernest - Emergency Medicine - 402-559-6802 - wtelken@unmc.edu - alt #:

701-330-3100 - degree: MD - address: UT 3202 UNMC Midtown (Zip 1150) - phone: 9-6802

**C. Participating Personnel:**

Baker, Susan J - Hyperbaric 02 Unit (HBO) - - subaker@nebraskamed.com - alt #:

402-552-2490 - degree: APRN - address: Clarkson Tower (Zip 68105)

Barksdale, Aaron Nathan - Emergency Medicine - 402-559-9994 -

aaron.barksdale@unmc.edu - alt #: 402-559-9994 - degree: MD - address: UT 3243 UNMC

Midtown (Zip 1150) - phone: 9-9994

Brailita, Daniel M - Int Med Infectious Diseases - 402-559-5443 - dabrailita@unmc.edu - alt

#: 402-559-5443 - degree: MD - address: MSB 5505 UNMC Midtown (Zip 5400) - phone:

9-5443

Etoll, Erin (Erin) M - Anesthesiology - 402-559-4081 - eetoll@unmc.edu - alt #:

402-559-4000 - degree: MD - address: BTH 2012 UNMC Midtown (Zip 7541) - phone:

9-4081



Fowler, Karen E - Hyperbaric 02 Unit (Hbo) - 402-552-2490 - kfowler@nebraskamed.com - alt #: 402-552-2490 - degree: RN - address: Clarkson Tower (Zip 68105) - phone: 402-552-2490

Fremming, Bradley (Brad) Allen - Anesthesiology - 402-559-4081 - brad.fremming@unmc.edu - alt #: 402-871-5797 - degree: MD, PharmD - address: ESH 3018C UNMC Midtown (Zip 7541) - phone: 9-4081

Gundabolu, Krishna - Int Med Oncology/Hematology - 402-559-8052 - krishna.gundabolu@unmc.edu - alt #: 402-559-8052 - degree: MBBS - address: BCC 4.12.301 UNMC Midtown (Zip 6840) - phone: 9-8052

Jensen, Chris (Chris) James - Family Medicine - 402-559-6982 - cjensenj@unmc.edu - alt #: 402-559-4000 - degree: MD - address: MSB 25103 UNMC Midtown (Zip 3075) - phone: 9-6982

Jones, Drea (Drea) D - Family Medicine - 402-559-0282 - andrea.jones@unmc.edu - alt #: 402-201-7268 - degree: MD - address: FNT 5005 Ames AVE (68104) - phone: 9-0282

Perry, Thomas R - Emergency Medicine HOME - 402-559-6802 - thomas.perry@unmc.edu - alt #: 402-559-4000 - degree: DO - address: UT 3202C UNMC Midtown (Zip 1150) - phone: 9-6706

Thacker, Jenny L - Emergency Medicine - 402-559-5413 - jthacker@unmc.edu - degree: MD - address: UT 3200 UNMC Midtown (Zip 1150) - phone: 9-5413

Winn, Dana A - Hyperbaric 02 Unit (Hbo) - 402-552-3336 - dwinn@nebraskamed.com - alt #: 402-552-2490 - degree: RN - address: Clarkson Tower (Zip 68105) - phone: 402-552-3336

**D. Lead Coordinator:**

Zimmerman, Brooklin K - Emergency Medicine - 402-559-5237 - brooklin.zimmerman@unmc.edu - alt #: 402-836-9405 - degree: MSN, BA, RN - address: UT 3231 UNMC Midtown (Zip 1150) - phone: 9-5237

**E. Coordinator(s):**

**F. Data/Administrative Personnel:**



**G. Are you a student or house officer?**

No

**4. Funding Source:**

**Check all that apply and provide the source of the funding.**

Cooperative Group:

Grant - Provide source:

Commercial - Provide company name:

Department of Defense

◆ Other - Provide source: Departmental Funds

Center for Clinical and Translational Research (CCTR)

**5. Contract:**

**Is there a contract or agreement associated with this study?**

No

**6. Funding Agency Deadline for IRB Approval:**

Yes

◆ No

**7. Study Sites:**

**A. Provide the names and locations of all study sites where this research will be conducted under the oversight of the UNMC IRB.**

UNMC

Hyperbaric Medicine

**B. Is this a multi-site study?**

No

**C. Does this study involve any international sites where the PI will either conduct or supervise the study?**

No

**8. Principal Investigator Assurance**

**The PI understands and accepts the following obligations to protect the rights and welfare of research subjects in this study:**

- **I certify that I have carefully reviewed this application and all supporting documents. I have determined that the application is accurate, complete and**



ready for submission to the IRB.

- I certify that I, and all listed research personnel, have the necessary qualifications, expertise, and hospital credentials to conduct this study in a manner which fully protects the rights and welfare of research subjects.
- I certify that all listed research personnel will be given a copy of the final IRB approved application and any other relevant study-related documents in accordance with their defined responsibilities.
- I recognize that as the PI it is my responsibility to ensure that this research and the actions of all research personnel involved in conducting the study will comply fully with the IRB-approved protocol, all applicable federal regulations, state laws, and HRPP policies.
- I recognize that it is my responsibility to ensure that valid informed consent/assent has been obtained, as appropriate, from all research subjects or their legally authorized representative (LARs). I will ensure that all research personnel involved in the process of consent/assent are properly trained and are fully aware of their responsibilities relative to the obtainment of informed consent/assent according to federal regulations, state laws, and HRPP policies.
- I certify that the minimum amount of protected health information (PHI) or other identifiers necessary will be used and disclosed to conduct this research study (if applicable). I will implement reasonable safeguards to protect the PHI/identifiers at all times.
- I will promptly inform the IRB of internal adverse events, as well as any unanticipated problems involving risk to the subjects or to others, as required within the time frame defined by HRPP policies. I will analyze each internal adverse event/reported problem to determine if it impacts the risk-benefit relationship of the study, the safety of the subjects, or informed consent.
- I will analyze each MedWatch/safety report to determine if it impacts the risk/benefit relationship of the study, the safety of the subjects, or informed consent. I will promptly submit external adverse event reports in accordance with HRPP policies.
- I will promptly inform the IRB if I become aware of 1) any complaints from research subjects, LARs, or others about research participation, 2) violations of



federal regulations or state law, 3) violations of the HIPAA Rule, or 4) violations of HRPP policies.

- I will promptly inform the IRB of the results of external audits performed by sponsors, Contract Review Organizations (CROs), cooperative groups, FDA, or other external groups.
- I will not initiate any change in protocol without IRB approval except when it is necessary to reduce or eliminate a risk to the subject, in which case the IRB will be notified as soon as possible.
- I certify that there are, or will be, adequate resources and facilities to safely initiate, carry out and complete this research at the study sites specified in Section I.7. This includes sufficient staff, funding, space, record keeping capability, and resources necessary to address adverse events and any unanticipated problems involving risk to the subject or others. If the necessary resources become unavailable I will promptly notify the IRB.
- I will promptly inform the IRB of any significant negative change in the risk/benefit relationship of the research as originally presented in the protocol and approved by the IRB.
- I understand that continuing review by the IRB is required at least annually in order to maintain approval status. I will maintain IRB approval as long as this study is active.
- I understand that I am responsible for appropriate research billing in accordance with UNMC Clinical Trial Professional and Technical Fee Billing Policy #8008 or applicable Children's Hospital & Medical Center policy.
- I certify that I and all other personnel listed in Section I.3A-E of the IRB Application have disclosed all potential financial conflicts of interest as required and are in full compliance with the UNMC Conflict of Interest Policy #8010 and HRPP Policy. I further certify that all potential financial conflicts of interest are appropriately managed in order to ensure protection of the rights and welfare of subjects.
- I will maintain all required research records on file and I recognize that representatives from the IRB, OHRP, HHS, FDA, and other Federal Departments or Agencies may inspect these records in accordance with granted authority.



- I understand that failure to comply with the Common Rule, applicable Subparts B, C, and D of HHS regulations at 45 CFR 46, applicable FDA regulations, the HIPAA Rule, applicable state law, HRPP policies, and the provisions of the IRB-approved protocol may result in suspension or termination of IRB Approval of my research project and/or other administrative or legal actions.

Cooper, Jeffrey Scott - 2025-03-12 07:13:09.003

## **9. Principal Investigator Financial Interest Disclosure**

### **A. As the PI, I declare:**

- ◆ I have no financial interest in this research.

I have a financial interest in this research.

### **B. As the PI,**

- ◆ I understand I must disclose any change in my financial interest during the course of this research within five (5) business days from the time the change becomes known.

### **C. As the PI who is ultimately responsible for the proper conduct of this research, I also certify that:**

- ◆ No Responsible Personnel have a financial interest in this research.

The Responsible Personnel listed below have informed me that they have a financial interest in this research.

### **D. I have informed all Responsible Personnel that if there is any change in their financial interests during the course of this study it must be disclosed within five (5) business days from the time the change becomes known.**

Cooper, Jeffrey Scott - 2025-03-12 07:13:09.003

## **11. Scientific/Scholarly Merit and Resource Review Certification**

### **A. Scientific Reviewer:**

Wadman, Michael Charles - Emergency Medicine - 402-559-6948 - mwadman@unmc.edu - alt #: 402-559-6948 - degree: MD - address: UT 3291 UNMC Midtown (Zip 1150) - phone: 9-6948

### **As the Scientific Reviewer,**

- ◆ I do not have a financial conflict of interest associated with this study.



**My signature certifies that this application has been reviewed for scientific/scholarly merit and available resources. It has been determined that the application merits consideration by the IRB based upon the following:**

- **The proposal has an acceptable level of scientific/scholarly merit which justifies the use of human subjects.**
- **The proposal has a sound research design in consideration of the stated objectives.**
- **The PI has the necessary qualifications, experience and credentials to conduct this research.**
- **The PI has or will have the necessary funding to support this research.**
- **There is or will be adequate physical space required for the research interventions at all study sites specified in Section I.7. In addition, there is or will be adequate laboratory and clerical support, data storage capability, and any other resources necessary to complete this research.**
- **At all study sites specified in Section I.7, there is or will be emergency equipment, personnel, or services necessary to respond promptly to adverse events or unanticipated problems involving risk to the subject or others.**
- **I will promptly notify the IRB if the necessary resources to support this research become unavailable.**
- **I am not listed as study personnel in Section I of this application.**

Wadman, Michael Charles - 2018-01-05 12:41:00.000

**Do you have any additional comments that you wish the IRB to consider during the review of this application?**

No

## SECTION II

### PROTOCOL ABSTRACT

**1. Provide a brief (less than 400 words) abstract of the research protocol.**

**This summary should include: 1) the title of the protocol, 2) a *brief* description of the purpose of the study, 3) eligibility criteria, 4) interventions and evaluations and 5) follow-up.**

Hyperbaric oxygen therapy in acute sickle cell pain crisis.

The purpose of this study is to explore if hyperbaric oxygen therapy would decrease hospital length of stay and pain associated with acute sickle cell pain crisis. Eligibility criteria include both female and males age 19 years or older with sickle cell who are in an acute pain crisis. Exclusions include pregnancy and a sickle cell crisis complicated by any acute significant concomitant factors/conditions (i.e., acute chest syndrome, acute MI/stroke). Interventions would be 1-3 hyperbaric oxygen sessions depending on response to the therapy. Each treatment session will be approximately two hours in length. Evaluation would be through patients' self assessment via the visual analog scale for pain level before and after treatments as well as tracking length of stay in the hospital.

### PURPOSE OF THE STUDY AND BACKGROUND

#### **2. Purpose of the Study**

**What are the specific scientific objectives of the research?**

The aim of the study is to assess if HBO treatment in patients experiencing sickle cell crisis would produce a decrease in pain and decrease in hospital length of stay.

#### **3. Background and Rationale**

**Describe the background of the study. Include a critical evaluation of existing knowledge, and specifically identify the information gaps that the project is intended to fill.**

The purpose of this study is to assess if HBO treatment in patients experiencing sickle cell crisis would produce a decrease in pain and decrease in hospital length of stay. Before starting the process of investigating this scientific question it is important to take a look back to see what previous studies and research has been done related to HBO and sickle cell disease. While doing this, several key literature pieces stand out. The first by Laszlo 1969 studied 5 sickle cell crisis patients and the effects HBO had on sickling and assessed for clinical symptom resolution. It was found that HBO did reduce reversible sickled cells and persisted for some time after treatment. In regards to clinical symptomatic relief, one patient had complete resolution of his associated hematuria and another had complete pain relief after HBO treatment. This study showed that HBO can reverse sickling and may have some clinical benefit, but this study was small (N=5) and was not randomized.



In 1971 Reynolds published a case report of a patient with refractory painful crisis who was successfully treated with HBO. This patient was initially given blood, 5 LPM oxygen therapy, fluid resuscitation, bicarbonate, and pain medications, and experienced no symptomatic relief. The patient was then treated with HBO and was found to be pain free afterwards. This case study was only one patient, but does give good reason to look into the possible benefit from HBO in the treatment of refractory sickle cell pain crisis.

In a study by Embury in 1984, they followed 3 sickle cell patients who were treated with continuous O<sub>2</sub> for 5 days. It was noted that during the oxygen treatment these patients had a reduction in EPO, reduced ISC and increase anemia. After treatment cessation, the patients then experienced a rebound increase in WBCs and ISC counts. It was also noted that 2 of the 3 patients had a painful crisis after completion of O<sub>2</sub> therapy. This study suggests that oxygen may be beneficial on a short term basis, but prolonged exposure may be harmful. HBO was not used in this study, but serves as a possible reason to limit HBO treatments to a responsible number of treatments. In addition, it raises the question that if WBCs have a role in vaso-occlusive crisis (VOC) as this study suggests, could HBOs known effect of leukocyte adhesion reductions play a role in mitigating this WBC increase? Zipursky (1992) studied the potential of oxygen therapy to reverse sickling in sickle cell disease. 50% oxygen delivered via venture mask was shown to reduce the number of reversible sickled cells but not irreversible sickled cells. During this time, some patients reported subjective symptomatic improvement, but not all. This study focused more on the objective number of RSC and ISC pre and post oxygen therapy and not pain relief though. Because this study showed reduced sickling it is implicated that HBO may both reduce sickling as well as provide symptomatic relief.

In vitro effects of HBO on sickled cells were studied by Mychaskiw in 2001, which looked at the possibility of reversing sickling in vitro in a hyperbaric chamber. Blood samples from 10 patients with sickle cell disease were left at room air for 2 hours to allow to sickling and then underwent HBO treatment. When compared with controls, there was no effect from HBO on the morphology of the sickled cells. This study is a good direct look at in vitro cellular effects of HBO on sickled cells, yet other in vivo study results contradict this.

In a study in 2012, Stirnemann looked at 9 patients who were in refractory VOC crisis and assessed their pain use as well as narcotic usage before and after HBO treatment. All 9 patients experienced pain reduction and decrease in morphine usage as a result of HBO therapy. This study took a direct look at VOC and HBO therapy, which suggest that HBO seems to be a viable option of VOC patients who are refractory to conventional therapy, but an N=9 is still a small sample size to draw a generalized conclusion about.

From this scholarly literature, many results suggest and point to the hypothesis that HBO may help ameliorate symptoms and have positive effects for sickle cell patients. However, no information has been gathered to date about how this may effect hospital length of stay. In addition, although a few studies did discuss pain reduction associated with HBO therapy, they are currently conflicting and all have too small of sample size to carry any weight when compared against each other. With the currently proposed research, it is a hope that a larger sample size be collected to help generalize this information to more patients.

Currently at UNMC/Nebraska Medicine, if a patient is identified as having sickle cell and experiencing an uncomplicated pain crisis that is not responding to acute treatment in the emergency department over the course of a few hours, that patient will be admitted to our hematology service. They will then continue to receive IV fluid administration, oxygen, and usually large doses of pain medications, until their pain subsides. Patient's labs such as CBC and CMP/CMP are monitored during this time for any acute changes. Once the patient's pain has subsided and no signs of complications such as infection, etc. are found, the patient is discharged with follow up in hematology clinic.

## CHARACTERISTICS OF THE SUBJECT POPULATION

### 4. Accrual

Is this study conducted solely at sites under the oversight of the UNMC IRB (e.g. UNMC, TNMC, CH&MC, UNO)?

Yes

**A. What is the total number of subjects (per group, as applicable) needed to complete the research in order to achieve the scientific objectives of the research?**

10

**B. What is the statistical or other justification for the total number of subjects needed to complete the research in order to achieve the scientific objectives of the research?**

Total number of subjects was determined by averaging out the number of sickle cell pain crisis patients that UNMC Emergency Department admits in approximately 6 months.

Our intent is to study ten subjects. We are initially consenting 30 as a potential subject pool as we cannot know ahead of time who will return in the inclusion criteria window to be study subjects. We will study the first 10 subjects that present and meet inclusion and exclusion criteria.

We anticipate rapidly accruing the initial 30 participants but cannot predict when such a participant will have a crisis and present for admission and study protocol. However,



inclusion criteria limits the time frame to two years. Therefore, we should have studied all ten subjects in less than three years from initiation. Study stops after studying ten subjects. If a subject drops out during the study, they are not replaced.

**C. Based on the anticipated number of screen failures and/or subject withdrawals, what is the maximum number of subjects that will need to be consented in order to achieve the scientific objectives of the research?**

30

**5. Gender of the Subjects**

**A. Are there any enrollment restrictions based on gender?**

Yes

**Provide justification.**

If a female is pregnant, she shall be excluded from the study due to lack of previous research on the ramifications and effects of HBO in the unborn fetus.

**6. Age Range of Subjects**

**A. What is the age range of the adult subjects?**

≥19 years old

**B. What is the rationale for selecting this age range?**

We choose 19 years old due to this being the age of majority in Nebraska, the aim of this study being the investigation of the adult population solely, and the lack of evidence of potential risk in the pediatric population.

**C. Will children (18 years of age or younger) be included in this research?**

No

**What is the justification for excluding children from participating in this research?**

Research is irrelevant to children (e.g. disease or condition rarely encountered in children). Knowledge being sought in the research is already available for children or will be obtained from another ongoing study.

A separate study in children is warranted and preferable.

♦ Insufficient data are available in adults to judge the potential risk in children.

Other. Explain.

**7. Race and Ethnicity**

**Are there any subject enrollment restrictions based upon race or ethnic origin?**



No

### **8. Vulnerable Subjects**

**A. Will any of the following vulnerable populations be allowed to participate in this research? Check all that apply.**

Pregnant individuals, fetuses or neonates (non-viable or of uncertain viability)

Prisoners

Children (< 19 years of age)

Decisionally-impaired persons

◆ None

**B. Will any other vulnerable population (critically ill patients, students or employees of the investigator, etc.) be specifically recruited for enrollment in this research?**

No

### **9. Inclusion Criteria**

**What are the specific inclusion criteria?**

Inclusion criteria for Initial Consent:

≥19 years old

Confirmed sickle cell disease diagnosis

Prior hospitalization for sickle cell crisis

Inclusion criteria for Pre-Treatment Consent:

≥19 years old

Confirmed sickle cell disease diagnosis

Currently in uncomplicated sickle cell crisis at the time of admission from the Emergency Department at Nebraska Medicine

Signed HAVOC initial consent

Prior hospitalization at Nebraska Medicine or BMC for sickle cell crisis no more than two years prior to signing pre-treatment consent

### **10. Exclusion Criteria**

**What are the specific exclusion criteria?**

< 19 years old, pregnant female, complicated sickle cell crisis present (i.e., concomitant MI, stroke, acute chest syndrome at time of presentation), previous enrollment in this pilot study (only enrolled in study once to avoid any additional bias), Untreated tension pneumothorax, current upper respiratory infections, history of seizures, emphysema with CO<sub>2</sub> retention, history of ear surgery, uncontrolled high fever, claustrophobia.

### **11. Pregnancy and Contraception Requirements**



**A. Are non-pregnant females of childbearing potential included in this research?**

Yes

**Are there any specific contraception requirements?**

No

**Provide justification. Check all that apply.**

No interventions are likely to be of risk to a fetus (including Category A drugs)

◆ Other. Explain. a pregnancy test will be obtained prior to HBO treatment. We will not enroll pregnant patients

**B. Are pregnant women included in this research?**

No

**a) Provide justification for excluding pregnant women.**

Intervention includes a Category B, C, D or X drug

Intervention includes a procedure expected to be of risk to the fetus (e.g. exposure to ionizing radiation, maximal exercise test)

◆ Research is not relevant to pregnant women (e.g. disease or condition rarely encountered in pregnant women)

Knowledge being sought in the research is already available for pregnant women or will be obtained from another ongoing study

A separate study in pregnant women is warranted and preferable

◆ Physiology of pregnancy precludes generalization to other populations

Other. Explain.

**b) Describe how pregnancy status will be assessed.**

◆ Self-report

◆ Blood pregnancy test

◆ Urine pregnancy test

N/A study includes males only

**C. Are breast feeding women excluded from participation?**

No

**METHODS AND PROCEDURES**

**12. Methods and Procedures Applied to Human Subjects**

**A. Are there any evaluations or tests that will be performed for the purpose of**

**determining subject eligibility which would not be routinely conducted as part of standard clinical care of the prospective subject?**

Yes

**Describe the evaluations or tests to determine subject eligibility:**

Pregnancy test for females of childbearing age/potential, which will be obtained only after subject consent has been signed. This test will be done prior to the first hyperbaric treatment. Further testing will not be done as it is not reasonable to suspect the patient becoming pregnant during a short hospital stay. Treatments will only be given over a few days of inpatient hospitalization.

**B. Describe sequentially all procedures, interventions, evaluations and tests.**

Will obtain either urine or blood from female subjects (depending on circumstances, other labs being collection, etc) and will test the specimen to see if the subject is currently pregnant at time of presentation. Other labs that may be drawn may include CBC, LDH, CMP and/or BMP. Interventions include HBO therapy sessions (1-3) depending on their response to the therapy. Each session will be approximately 2 hours in length at 2.5 ATM. During the session, there will be at least one HBO certified physician, and two nursing staff present. If for some reason, a subject is unable to tolerate the full 2 hour session, at any time they may stop descent in the chamber and "ascend" which takes approximately 2 minutes in an emergency or 10 minutes routinely. This will occur during normal HBO clinic hours. Sessions will be scheduled around regularly scheduled HBO appointments, as not to inconvenience other patients. There will be a minimum time between HBO sessions of 4 hours. In addition to HBO therapy, interventions may include oxygen via nasal cannula or nonrebreather, analgesia administration via PO, IV or IM (morphine, dilaudid, fentanyl, oxycodone, hydrocodone, etc) and fluid administration via PO and/or IV. Evaluations will be done by visual analog scale measurements of pain, amount of narcotics used during stay and length of stay in the hospital. This data from the enrolled 10 subjects will be compared to extracted data from EPIC of the same previous admissions, pain medications, and hospital admission days. Pain assessments will occur at initial ED presentation (already a standard of care in ED) and then every morning of admission on morning rounds from that point on until discharge. Pain completely resolved or max session number of 3 will be used as standard to not do any further HBO therapies. With this being a pilot study, and only enrolling 10 subjects, it will be unlikely we reach a "statistically significant" figure, but a 50% reduction in narcotic usage would be a meaningful clinical reduction.

Our HBO policy and procedure is to check finger stick blood glucose within 30 minutes prior to treatment and immediately after treatment. We do not treat if the blood sugar is below 120. It is not necessary or possible to check while inside the chamber.



**C. Identify all procedures, interventions, evaluations and tests that are:**

**1) Performed solely for research purposes.**

HBO therapy

Our patients will receive 1-3 hyperbaric oxygen sessions depending on their response to the therapy. Each session will be approximately 2 hours in length at 2.5 ATM. Minimum time between HBO sessions of 4 hours.

**2) Performed more frequently than they would be if the subject was not participating in the research.**

None

**3) Performed on the subjects in the course of their normal clinical care (i.e. for diagnostic or treatment purposes) where the data are used for research.**

We will be collecting data on length of stay, analgesic dosing, pain scale, complications, and tracking routine labs as ordered by ED and Hem/Onc e.g CBC, LDH

**D. Does this research involve genetic testing?**

No

**E. Will any un-used human biological material (HBM) be used to create a tissue bank for future research?**

No

**F. Describe briefly the statistical methods used to analyze the data.**

**Primary Objective/Hypothesis:**

To establish the efficacy / promise of hyperbaric oxygen therapy in reducing the impact of sickle cell pain crisis on patients.

Primary hypothesis: Hyperbaric oxygen therapy will result in a reduction in pain, length of stay, and narcotic dosage when compared to earlier admissions without hyperbaric oxygen treatment.

**Sample size.** Because this is a pilot study, the sample size is chosen to be obtainable within the time constraints of the study period and to be within the range of sizes discussed in Hertzog<sup>1</sup> in order to obtain estimates precise enough for pilot study aims. A sample size of 20 admitted patients with at least one previous admittance for sickle cell pain crisis and no previous hyperbaric oxygen therapy will be obtained by convenience.

**Setting.**

**Data Analysis.** As a pilot study, this study is underpowered for statistical hypothesis testing,



and analyses will focus on descriptive statistics, and estimation of effect sizes to power a future randomized controlled trial. To address the primary objective and assess patient availability for the intervention proportions, ranges, means, and standard deviations will be employed. To determine if there was a clinically relevant effect of the therapy the mean (standard deviation) and median (interquartile range) of the difference scores between the previous and current admission will be examined.

**Aside:**Reference 2 gives estimated standard deviations for LOS of around 6.25; and Opioid dose of 182.93 mg. Reference 3 gives a standard deviation estimate for the visual analog scale for pain of roughly 30 mm; based on a 10 cm (100 mm) line with anchors at each end.

References:

1. Hertzog, M A. (2008). Considerations in Determining Sample Size for Pilot Studies. *Research in Nursing & Health*. 31: 180-191.
2. Ballas, S K., et al. (2010). Hydroxyurea and Acute Painful Crises in Sickle Cell Anemia: Effects on Hospital Length of Stay and Opioid Utilization During Hospitalization, Outpatient Acute Care Contacts, and at Home. *J Pain Symptom Manage*. 40(6): 870-882.
3. Hawker, G A., et al. (2011). Measures of Adult Pain Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care & Research*. 63(11): 240252.

**G. Indicate the study design/phase by checking the appropriate box(s).**

Phase I

Phase I/II

Phase II

◆ Phase II/III

Phase III

Phase IV

Other:

Case-Control

Cohort

Cross-sectional

Randomized, parallel group

Randomized, cross-over

Placebo-Controlled

Single Blind



Double Blind

Triple Blind

**DRUGS, BIOLOGIC DRUGS AND DEVICES**

**13. Drugs and Biologic Drugs**

**A. Does this research involve an investigational drug or biologic drug?**

No

**B. Does this research involve an FDA-approved and marketed drug or biologic drug?**

No

**14. Devices**

**A. Does this research involve an investigational device?**

No

**B. Does this research involve an FDA-approved and marketed device?**

Yes

**CONFIDENTIALITY AND PRIVACY**

**15. Confidentiality and Privacy**

**A. Will research data be stored:**

**1) On a secure server at UNMC/TNMC/CH&MC/UNO?**

Yes

**2) On a local hard drive?**

No

**3) On a portable computer?**

No

**4) On a flash drive?**

No

**5) In a database accessible through the internet?**

No

**6) In hard copy?**



No

**7) Other.**

No

**B. Will any of the following subject identifiers be recorded (at any time) in association with the research data?**

Yes

**1) Indicate the subject identifiers that will be recorded. Check all that apply.**

◆ Name

Postal address information: street address, city, county, precinct, ZIP code

◆ DATES (e.g. date of study visit, date of sample collection, birth, admission, discharge)

Telephone numbers

Fax numbers

Electronic mail addresses

Social Security numbers

◆ Medical Record numbers

Health plan beneficiary numbers

Account numbers

Certificate/license numbers

Vehicle identifiers and serial numbers, including license plate numbers

Device identifiers and serial numbers

Web Universal Resource Locators (URLs)

Internet Protocol (IP) address numbers

Biometric identifiers, including finger and voice prints

Full face photographic images [and any comparable images]

No identifiers will be maintained

**2) Will a unique subject identifying number, characteristic or code be used to protect the confidentiality of the data? This includes codes assigned by the investigator to link data to other identifiers like the subject's name or medical record number.**

Yes

**a) Where will the key, that links the unique subject identification code to the subject's name or other identifier, be stored?**

On a secure server at UNMC.

**3) What is the justification for recording the specific identifiers listed above?**

Schedule appointments

◆ Collect continuous clinical information from the medical records

Follow-up with subjects

Link stored tissue with subject identification for it to be withdrawn in the future if requested

Other. Explain.

**4) How long will the subject identifiers be maintained in association with the research data?**

Subject identifiers will be maintained in association with the research data until conclusion of the study which is approximated at one year.

**5) How will the research data be archived or destroyed when the data is no longer required?**

Information will be kept on a secure server on campus and after the end of the study, information will be deleted from folder and ITS will be consulted to ensure all traces of pt information/data is erased properly

**6) Will research data that contain subject identifiers be disclosed to any other investigators at UNMC, TNMC, UNO or CH&MC who are not listed in Section I of this application?**

No

**7) Will research data that contain subject identifiers be disclosed to any investigators outside of UNMC, TNMC, UNO or CH&MC?**

No

**8) Will research data that contain subject identifiers be disclosed to any commercial sponsor, contract research organization (CRO) or Data and Safety Monitoring Board (DSMB)?**

No

**9) Will research data that contain subject identifiers be disclosed to any other external organization or entity (e.g., NCI cooperative groups)?**

No

**10) Will research data be shared with third party payers?**

No

**C. What provisions will be in place to protect the subject's privacy?**



- ◆ Obtaining consent in a private conference room or area
- ◆ Ensuring that only personnel listed on the IRB application Section I.3(A-E) are present during the consent process
- ◆ Ensuring that the fewest number of individuals possible are aware of the subject's participation in the research.
- ◆ Ensuring that the research activities are performed in as private of a place as possible Other. Explain.

**D. Does this research involve data banking at UNMC, TNMC, UNO or CH&MC for future research that is not related to this study?**

No

**E. Does this research involve data banking by an outside organization (e.g. NCI Cooperative Group, pharmaceutical company) for future, unspecified research that are not integral to the current research?**

No

## **RISK/BENEFIT ASSESSMENT**

### **16. Potential Risks**

**What are the potential risks associated with each research procedure, intervention, evaluation and/or test? If data are available, estimate the probability that a given harm may occur and its potential reversibility.**

Hyperbaric oxygen therapy is generally a safe procedure. Complications are rare. However, this treatment does carry some possible risks which include temporary nearsightedness (myopia) caused by temporary eye lens change, middle ear injuries (including leaking fluid and eardrum rupture) due to increased air pressure, lung collapse caused by air pressure changes (barotrauma), seizures as a result of too much oxygen (oxygen toxicity) in the central nervous system and, in certain circumstances, fire (due to the oxygen-rich environment of the treatment chamber).

### **17. Risk Classification**

**What is the overall risk classification of the research?**

Minimal risk

- ◆ Greater than minimal risk
- Significant risk

### **18. Minimization of Risk**

**A. Will the research utilize procedures already being performed on the subjects for**

**diagnostic or treatment purposes?**

No

**B. Describe how the subjects of the research will be monitored by the investigators and other research personnel to ensure their safety.**

All pts will be in-patient at UNMC during the hyperbaric oxygen therapy. They will be monitored before the therapy by the admitting physician service, during the therapy by specially trained HBO physicians and support team, and after the treatment again by the admitting team. All vitals, response to therapy and safety of pts will be closely monitored through all parts of patients care.

**C. Describe the process by which the PI will be informed and how the PI, in turn, will inform other research staff about events concerning subject safety (including (a) interim results; (b) adverse events; (c) unanticipated problems involving risks to subjects or others; (d) noncompliance; (e) complaints).**

**1) At UNMC/TNMC/CH&MC and/or UNO: Check all that apply.**

Not applicable. The PI is the only person listed in Section I of the IRB Application.

♦ By email or campus mail (for events which do not constitute immediate subject safety hazards)

♦ By phone

♦ By in-person meeting

By scheduled submission of case report forms

Other. Explain.

**2) At external study sites under the oversight of the UNMC IRB as applicable: Check all that apply.**

By email or mail (for events which do not constitute immediate subject safety hazards)

By phone

By in-person meeting or teleconference

By scheduled submission of case report forms

Other. Explain.

♦ Not Applicable

**D. Describe the auditing plan for research conducted:**

**1) Within the Organization (UNMC, TNMC, UNO or CH&MC), identify who will conduct the audits and specify the audit frequency.**

Auditing will occur by Dr. Michael Wadman, chair of the Emergency Department every six months and any violations or unanticipated problems involving risks to the subjects or others will be submitted to the IRB as required.

**2) At external study sites under the oversight of the UNMC IRB, identify who will conduct the audits and specify the audit frequency.**

N/A

**E. Is there is an independent DSMB for this study?**

No

**Describe the data monitoring plan.**

Data will be monitored by Dr. Cooper, the PI. He will carefully and continually assess all processes and outcomes for patient safety as each patient is admitted and throughout the treatment process.

**1) Who will perform the ongoing data and safety analysis?**

Dr. Cooper

**2) What is the frequency of data analysis?**

Data will be analyzed each time a patient is admitted from the UNMC emergency department and the proposed treatment plan is initiated. The exact frequency number will depend on when and how many patients present to the emergency department and consent to be a part of the research study.

**F. Describe the specific criteria by which the investigator would withdraw individual subjects from the research (for example, medical criteria, such as specific toxicity or lack of efficacy or non-medical criteria, such as non-compliance).**

Patients will be withdrawn from the research if they experience an oxygen toxicity related seizure during HBO treatment, or if a subject decides to not continue with HBO treatment after initiation (claustrophobia, etc).

**G. Describe the specific criteria for halting or early termination of the study (for example statistical evidence of unacceptable toxicity or early demonstration of efficacy or lack of efficacy).**

The study may be halted or terminated early if continuous data analysis proves that the proposed hyperbaric oxygen therapy causes any harm, i.e., worse pain, or longer hospital stay compared to the current standard of treatment for sickle cell crisis.

**H. Describe plans and resources available to promptly address any subject injury.**

If a subject should suffer a research related injury during the study, they will already be admitted at UNMC and the admitting team and/or the hyperbaric team will promptly identify, treat and resolve the related concerns medically.

**19. Potential Benefits to the Subject**

**Are there potential benefits to the subjects that may reasonably be expected from participation in the research?**

Yes

**Describe.**

Participants may not receive any benefit from being in this research study. Possible benefits may include decreased pain and shortened length of stay in the hospital related to the patient's sickle cell pain crisis.

**20. Potential Benefits to Society**

**What are the anticipated benefits (i.e., value) to society that may reasonably be expected to result from this research?**

Possible benefits to other people include the advancement of medical knowledge as well as a change in therapy in the treatment of sickle cell crisis patients.

**21. Alternatives to Participation**

**A. How do the study procedures or courses of treatment differ from the care that the subject might receive were he/she not to participate in the research?**

Instead of being in this research study, patients can choose not to participate. Alternatives to being in this research study include receiving the current standard of care without hyperbaric oxygen therapy. This includes pain management with analgesics as well as proper fluid resuscitation and oxygenation via nasal cannula/nonrebreather. Taking part in this study is completely voluntary. If patients decide not to participate, it will not affect their current or future relationship with the University of Nebraska Medical Center. If they decide to participate, they may withdraw at any time.

**B. Are there any reasonably available alternatives in the non-research context which would have the potential for providing the same benefits (treatment or other) to subjects?**

Not applicable. There are no direct benefits to subjects; the alternative is to not participate in the research.

♦ Yes. Describe: benefits may include decreased pain and shortened length of stay in the hospital related to patient's sickle cell pain crisis.

No. Explain:

**C. Would any of the study procedures or courses of treatment in the protocol be available to the prospective subject if they elected not to participate?**

No



**Explain.**

Hyperbaric oxygen therapy is not considered conventional care at UNMC for treatment of sickle cell crisis and is not currently in the treatment protocol. Therefore, if a prospective subject elects not to participate, it is unlikely that they would receive HBO therapy.

**D. How do the risks of the research compare with the risks of alternative procedures or courses of treatment described above?**

The risks associated with hyperbaric oxygen therapy are limited compared to the alternate course of treatment. Most individuals handle HBO therapy without issue and they will still receive at baseline the standard of care treatment for a sickle cell crisis in addition to HBO therapy.

**E. How do the anticipated benefits of the research compare with the benefit of alternative procedures or courses of treatment described above?**

Hyperbaric oxygen therapy has no guaranteed benefits compared to alternate courses of treatment, but does have the potential benefit of decreasing pain associated with the sickle cell crisis as well as decreased length of stay in the hospital compared to the alternate course of treatment. Patients will still receive the baseline therapy for sickle cell in addition to HBO therapy, so there should be no disadvantage of participation in the research when compared with available alternatives.

**FINANCIAL OBLIGATIONS AND COMPENSATION**

**22. Financial Obligations of the Subject**

**A. Who will pay for procedures and treatments performed solely for research purposes? Check all that apply.**

Sponsor

Grant

CRC, CCTR

Costs or fees waived by TNMC, UNMC- P, CH&MC or CSP

Subject's health insurance

Medicare/Medicaid

◆ Department/Section funds

Other. Explain.

Subject

**B. Are there any other financial obligations that the subject will incur as a result of participating in the study (e.g. travel expenses, meals, supplies)?**

No



**23. Compensation to the Subject for Participation**

**Will the subject receive any compensation for participation?**

No

**PRIOR REVIEW**

**24. Prior IRB Review**

**A. Has this study (or one substantially similar) been previously submitted to the UNMC IRB (or the Joint Pediatric IRB) and then withdrawn by the investigator for any reason?**

No

**B. To the best of your knowledge, has this study (or one substantially similar) been considered by another IRB and not granted approval?**

No

**SUBJECT IDENTIFICATION & RECRUITMENT**

**25. Method of Subject Identification and Recruitment**

**A. Will prospective subjects be identified through initial contact by the investigator?**

Yes

**1) Identified through: Check all that apply.**

◆ Clinic

◆ Hospital inpatient units

Previous research participants

◆ Investigator, clinic or hospital-maintained databases or registries

Other. Explain.

**2) Describe how the research staff has ethical access to the potential subjects?**

The ED research coordinator will utilize the opt-in research database to contact qualifying patients using the approved email message and phone script and following the CRC SOP-51.

Treating providers will also speak with patients during a follow up clinic appointment, inpatient admission, and/or ER discharge.

**B. Will prospective subjects make the initial contact with the research personnel to inquire about the study?**

No



**C. Will this study be listed in the clinical trial registry at [www.clinicaltrials.gov](http://www.clinicaltrials.gov)?**

Yes

**Provide the NCT number.**

NCT03412045

## **OBTAINMENT OF INFORMED CONSENT**

### **26. Waiver or Alteration of Informed Consent**

**Is a waiver or alteration of consent requested for either 1) all of the subjects or 2) a subset of subjects?**

No

### **27. Waiver of a Signed Consent Form**

**Is a waiver of the requirement to obtain a signed consent form requested?**

No

### **28. Capacity to Consent**

**A. At the time of initial consent, will all subjects have the capacity to give informed consent?**

Yes

**B. Is there a reasonable likelihood that some subjects may lose the capacity to continue to provide informed consent during the course of the study?**

No

### **29. Process of Informed Consent for Competent Adult Subjects**

**A. When will the prospective subject be approached relative to their actual participation in the study?**

Participation in the HAVOC trial requires two consents - Initially while not experiencing acute pain and again when admitted for uncomplicated sickle cell crisis prior to HBO treatment.

Consent #1

The ED research coordinator will work with the VCR Recruitment team and EHR core to utilize the opt-in research database to contact qualifying patients. Treating providers will also consent patients meeting HAVOC inclusion criteria during a routine clinic appointment, inpatient admission, and/or ER discharge. Patients will not be approached while experiencing acute pain.

Unfortunately, utilizing the opt-in research database has not been successful. Despite four attempts and various ICD-10 code combinations, data pulls have been inconsistent. The issue appears related to provider entry error when assigning the ICD-10 code specific to sickle cell disease and hospital admission designation. The VCR Recruitment team and EHR core suggests further screening the patients on the opt-in list prior to contact to ensure only patients meeting the inclusion criteria are approached and others are not contacted unnecessarily.

Additional screening would require IRB approval to include patient MRNs on the opt-in research database list. If IRB approved, the research coordinator would use the opt-in list to screen the patients EHR to verify a sickle cell disease diagnosis and a recent hospitalization for sickle cell crisis. Once it is confirmed the patient meets the study specific inclusion criteria, the coordinator would contact qualifying patients using the approved phone script and following the CRC SOP-51.

Very few patients would be affected by this recruitment exception. Historical data pulls have included less than 40 patients. The research coordinator would be the only person on the study team screening patients.

#### Consent #2

When a previously consented patient is admitted for sickle cell crisis, the patient will sign a second consent in the emergency room or their assigned hospital room.

#### **B. Where will informed consent be obtained, and how will the environment be conducive to discussion and thoughtful consideration?**

In person consent, whether consent #1 or #2, will be obtained in the privacy of the patient's own closed door emergency department or clinic/hospital room.

Patients from the research opt-in list wanting to enroll will sign consent either in person or remote, depending on personal preference and potential burden or delay of enrollment caused by meeting in person. If remote, the patient will choose their own private setting and the consenting provider will be in a private office or clinic space. The remote consent process will follow UNMC policy 5.3.

#### **C. Who will be involved in the process of consent and what are their responsibilities?**

##### Consent #1

The providers listed as eligible to consent will initially consent patients during a routine clinic visit, inpatient admission, and/or ER discharge.

Patients on the opt-in recruitment list will be contacted by the research coordinator using only the approved script and following CRC SOP-51. If interested in study participation after the initial phone call with the study coordinator, a consent form and HBO patient information handout will be mailed or emailed to the prospective subject. After approximately one week, a provider on the study team and the research coordinator will follow up with the subject to answer any questions. The consent may be signed at that time or time will be scheduled to sign the consent in person.

#### Consent #2

The emergency medicine and HBO providers listed as eligible to consent will re-consent the subjects in the emergency room or patient's room.

A One Chart inbox alert and email will notify the study PI and research coordinator of the admission of a subject enrolled in the study. The PI and/or research coordinator will arrange for the subject to sign the second consent with an available consenting provider.

During both consenting opportunities, the providers will explain the research, answer all questions the potential subject may have, and demonstrate/illustrate all research processes with subject during the process of consent. UNMC HRPP policy 5.1 and 5.3 will be followed by all involved in the consent process.

#### **D. How much time will be allotted to the process of consent?**

The time allotted to the process of consent may vary between patients in the study. There is no acute emergency to consent patients within a strict time allotment, and patients will be given as much time as they need to process the study within reason. Ideally patients will decide on consent within a few hours of being in the emergency department.

#### **E. How will the process of consent be structured for subjects who are likely to be more vulnerable to coercion or undue influence?**

Patients who are likely to be more vulnerable to coercion or undue influence will be encouraged to involve the subject's family or friends, teaching aids (such as drawings) and verbally reading and further explaining the consent to the subject.

An HBO patient information handout will be used during the consenting process. The handout is a Flesch-Kincaid level 11.0. The handout is a 8.0 level when the words hyperbaric, atmospheric, chamber, and oxygen are eliminated but having these words included is important for patient understanding and communication and are therefore defined in the handout.

#### **F. Will non-English speaking subjects be enrolled in this research?**



Yes

**Explain how you will ensure that the language used in the consent process and consent form is understandable to the subjects.**

There are no known non-English speaking patients with sickle cell, but if one appears to the ED, they will have the same option as English speaking patients to enroll in the research. We will have a translator help thoroughly explain the consent form and what the research entails. At this time it is not anticipated that a substantial number of subjects will not speak English. Therefore, no consent form in an alternate language will be submitted at this time.

**G. How will it be determined that the subject understood the information presented?**

Prospective subjects will demonstrate that they understand the information that we provide by repeating back, in their own words, the process of the study they are potentially going to enroll in and possible risks.

**H. Will there be a formal process of on-going re-consent (over and above re-consent associated with changes in protocol)?**

No

**30. Documentation of Informed Consent and Assent**

**List who will sign the consent form as the "Person Obtaining Consent".**

Baker, Susan J.

Barksdale, Aaron Nathan

Coffey, Shaila Kay

Cooper, Jeffrey Scott

Etoll-Jones, Erin M

Fremming, Brad Allen

Gundabolu, Krishna

Jensen, Chris James

Jones, Drea D

Perry, Thomas R

Thacker, Jenny L

**31. Consent Forms and Study Information Sheets**

**Indicate the type of consent forms and study information sheets to be used in this research. Check all that apply.**

- ◆ Adult consent form
- Legally authorized representative (LAR) consent form
- Parental/Guardian consent form
- Youth study information sheet
- Child study information sheet
- Adult study information sheet (decisionally-impaired)
- Screening consent form
- Addendum consent form
- ◆ Other. Explain. Two separate adult consent forms - first consent prior to sickle cell crisis; second consent during hospitalization for crisis

**32. Information Purposely Withheld**

**Will any information be purposely withheld from the subject during the research or after completion of the research?**

No

**RESOURCES****33. Describe the resources available to safely conduct this study at each study sites specified in Section I.7.**

Resources available to conduct this study safely include:

1. Funding: Departmental funds
2. Physical Space: Hyperbaric chambers in the Hyperbaric Unit at UNMC
3. Adequate lab and clerical support include the In-patient team that would already be taking care of patient no matter if they decide to participate in research or not. Also includes Hyperbaric staff that is fully staffed from 0700 to 1700 which can accommodate the research participants. If patients come in after hours, patient's hyperbaric treatment will wait until next available open time for treatment during hyperbaric department hours of operation.
4. Data storage capability and security: All data will be kept on secured University of Nebraska network and will not be shared outside of the pertinent team
5. Availability of equipment, person and services necessary to respond promptly to adverse events is always present during hyperbaric oxygen therapy on a daily basis, and will continue to be in place for participants of the study. In addition, patient will be under the care

of the admitting service and will access to care while in patient 24/7.

## LITERATURE REVIEW

### 34. References

**Provide a full listing of the key references cited in the background (Section II.3). The references should clearly support the stated purpose of the study.**

Embury, Stephen H., Joseph F. Garcia, Narla Mohandas, Rukmani Pennathur-Das, and Margaret R. Clark. "Effects of Oxygen Inhalation on Endogenous Erythropoietin Kinetics, Erythropoiesis, and Properties of Blood Cells in Sickle-Cell Anemia." *New England Journal of Medicine* 311.5 (1984): 291-95. Print.

Laszlo, John, William Obenour, and Herbert A. Saltzman. "Effects of Hyperbaric Oxygenation on Sickle Syndromes." *Southern Medical Journal* 62.4 (1969): 453-56. Print.

Mychaskiw, George, Stephen A. Woodyard, Claude D. Brunson, Warren S. May, and John H. Eichhorn. "In Vitro Effects of Hyperbaric Oxygen on Sickle Cell Morphology." *Journal of Clinical Anesthesia* 13.4 (2001): 255-58. Print.

Reynolds, J. D. "Painful Sickle Cell Crisis. Successful Treatment with Hyperbaric Oxygen Therapy." *JAMA: The Journal of the American Medical Association* 216.12 (1971): 1977-978. Print.

Stimemann, Jerome, Edouard Letelier, Nazmiye Aras, Marc Borne, Louis Brinquin, and Oliver Fain. "Hyperbaric Oxygen Therapy for Vaso-Occlusive Crises in Nine Patients with Sickle-Cell Disease." *Diving and Hyperbaric Medicine* 42.2 (2012): 82-84. Print.

Zipursky, Alvin, Isabelle Robieux, Elizabeth Brown, Dian Shaw, Hugh O'Broovich, James Kellner, Max Coppes, Gideon Koren, and Nancy Olivieri. "Oxygen Therapy in Sickle Cell Disease." *American Journal of Pediatric Hematology/Oncology* (1992): 222-28. Print.



## **SECTION III**

### **SUBMISSION DEADLINE**

#### **A. Full Board Review:**

The IRB meets twice monthly, on the first and third Thursday of the month, with the exception of January and July when the IRB meets only on the third Thursday of the month. No more than 15 applications (i.e., initial review of a new study, re-review of a tabled study) will be reviewed at each meeting. All reviews are performed on a first-come first-served basis. The IRB meeting schedule and deadline dates can be found on the IRB website at [www.unmc.edu/irb](http://www.unmc.edu/irb).

#### **B. Expedited Review**

Applications that qualify for expedited review have no submission deadline and can be reviewed independent of the IRB meeting schedule. Call the Office of Regulatory Affairs for assistance in determining if your study meets the requirements for expedited review.

### **SUBMISSION CHECKLIST**

#### **Check all that apply.**

- ◆ Subject recruitment material  
UNMC and NM - Pharmacy and Therapeutics (P&T) Committee Investigational Drug Study Registry and/or Marketed Drug Form  
Investigational Device Review Committee (IDRC): Review by the IDRC is required for all protocols involving the use of investigational or marketed devices.  
Performance site approval for all non-UNMC, TNMC, UNO and CH&MC sites
- ◆ Copy of all questionnaires, surveys, assessment tools, and other relevant materials  
Clinical Trial Master Matrix as required by UNMC and TNMC.
- ◆ Detailed protocol  
Investigator's brochure  
Grant Application  
IRB Review Fee Form for all commercially sponsored research projects.  
UNMC Disclosure of Potential Conflict of Interest Form for the Principal Investigator if a financial interest has been declared in Section I.10.
- ◆ UNMC Disclosure of Potential Conflict of Interest Form for any responsible personnel with a financial interest declared in Section I.10.
- Other
- No attachments



## **ADDITIONAL REVIEW REQUIREMENTS**

**Final IRB approval and release of studies is contingent upon approval by the following UNMC committees or departments. Check the appropriate boxes:**  
**UNMC and NM - Pharmacy & Therapeutics (P&T) Committee** (Required for studies involving drugs)

**Fred & Pamela Buffett Cancer Center Scientific Review Committee (SRC)** (Required for studies involving cancer)

**Institutional Biosafety Committee (IBC)** (Required for studies involving the use of gene transfer and vaccines)

**Investigational Device Review Committee (IDRC)** Review by the IDRC is required for all protocols involving the use of investigational or marketed devices

**Billing Grid** (Required for all studies involving billing for hospital/clinic services)

**Coverage Analysis** (Departments requiring this analysis have been specified by the Organization)

**Conflict of Interest (COI) Management Plan** (Required for all studies with declared COI by study personnel)

**Sponsored Programs Administration (SPA)/UNeHealth** grants and contracts

**Pathology approval** for collection of tissue samples required for this study

**Radiation Committee Approval**

**Other Review**

◆ **None of the above organizational requirements apply to this study**



**ADDENDUM R  
Investigational Devices**

**Title of Protocol**

(HAVOC) Hyperbaric Oxygen Therapy in Sickle Cell Pain Crisis

**Principal Investigator**

Cooper, Jeffrey Scott - Emergency Medicine - 402-552-2490 -  
jeffrey.cooper@unmc.edu

**A. Does this research involve a non-FDA approved investigational device?**

No

**B. Does this clinical investigation involve an FDA-approved and marketed device which will be used for an unapproved use?**

Yes

**1. Identify the marketed device used in the investigation.**

Hyperbaric Oxygen Therapy Chamber

**2. Describe the marketed device used in the investigation.**

The hyperbaric oxygen therapy chamber will be used to "dive" patients who are admitted for a sickle cell crisis. Hyperbaric oxygen therapy chamber is currently FDA approved for: air/gas embolism, carbon monoxide poisoning, Clostridial myositis/myonecrosis, crush injury/compartament syndrome/acute traumatic ischemia, decompression sickness, enhancing healing of certain wounds, exceptional blood loss anemia, necrotizing soft tissue infections, refractory osteomyelitis, delayed radiation injury, skin graft/flaps, thermal burns, and intracranial abscess. Hyperbaric oxygen therapy is used off label for sickle cell crisis. Off label use of any FDA approved medical device is allowed by the FDA for a licensed physician.

**3. Is the marketed device as used in this investigation a Non-significant Risk Device (NSRD)?**

Yes

**a) Provide rationale for why the marketed device is an NSRD.**

Hyperbaric oxygen therapy is a NSRD because it is noninvasive, does not require invasive sampling procedure that presents significant risk, does not introduce energy into the subjects, and is not used as a diagnostic procedure. The side effects of hyperbaric oxygen



therapy have been reviewed by the FDA and has been approved.

**b) Is the NSRD under an:**

Yes

**4. Indicate the stage or type of the investigation by checking the appropriate box.**

Stage I

◆ Stage II

Stage III

Nonclinical study

Other. Indicate type of investigation.

**5. Describe oversight procedures in place for departments, sections, or operating rooms where devices are used which provide for independent monitoring of the storage and dispensing of devices as well as required record-keeping.**

Oversight of the procedures when the device will be used will be by the hyperbaric department staff, RN's and the attending physician who is in charge of the department at that time.