Study Protocol with Statistical Analysis Plan

Protocol: Hyperbaric Oxygen Therapy to Prevent Complications after Lower Limb Amputation

NCT #: NCT04717557

Date: February 16th, 2024

DUHS IRB Application (Version 1.17)

General Information

***Please enter the full title of your protocol:**

Hyperbaric Oxygen Therapy to Prevent Complications after Lower Limb Amputation

***Please enter the Short Title you would like to use to reference the study:**

Hyperbaric Oxygen and Amputations
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

Add Study Organization(s):

List Study Organizations associated with this protocol:

Primary Dept?	Department Name
◉	**DUHS** - Anesthesia
○	**DUHS** - Duke Default Department

Assign key study personnel (KSP) access to the protocol

*** Please add a Principal Investigator for the study:**

(Note: Before this study application can be submitted, the PI MUST have completed CITI training)

Moon, Richard

3.1 If applicable, please select the Key Study personnel: (Note: Before this study application can be submitted, all Key Personnel MUST have completed CITI training)
*** Denotes roles that are not recognized in OnCore. Please select an appropriate role that is recognized in all clinical research applications (iRIS, OnCore, eREG, etc.)**

A) Additional Investigators, Primary Study Coordinator (CRC), and the Primary Regulatory Coordinator (PRC):

Allen, Justin
Co-PI

B) All Other Key Personnel

Allen, Justin
Sub-Investigator
Cooter Wright, Mary
Analyst*

Covington, Derek
Study Coordinator (CRC/CRNC/RPL)
Cox, Mitchell
Sub-Investigator
Derrick, Bruce
Sub-Investigator
Ellis, Mary
Sub-Investigator
Gregory, Thomas
Sub-Investigator
Lauer, Laura
Sub-Investigator
Long, Chandler
Sub-Investigator
Makowski, Matthew
Sub-Investigator
Natoli, Michael
Regulatory Coordinator
Pack, Neena
Research/Physician Assistant
Pack, Neena
Clinical Research Specialist/Study Assistant
Southerland, Kevin
Sub-Investigator
Stolp, Bryant
Collaborator
Vallee, Isabelle
Sub-Investigator

***Please add a Study Contact:**

Allen, Justin
Moon, Richard
Natoli, Michael
Pack, Neena

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g., The study contact(s) are typically the Principal Investigator, Study Coordinator, and Regulatory Coordinator.)

Oncore

Please select the Library for your Protocol:

This field is used in OnCore and determines the Reference Lists, Forms, Protocol Annotations, Notifications, and Signoffs available for the protocol. Protocols that require reporting to the NCI (National Cancer Institute), must select the Oncology library.

- ○ Oncology
- ◉ Non-Oncology

Protocol Application Type

Select the type of protocol you are creating:

Please see additional criteria and information in the policy titled, "Reliance on the IRB of Another Institution, Organization, or an Independent IRB", on the **IRB web site**.

- (●) Regular Study Application - Most common. The IRB will determine if the study is eligible for expedited review or requires full board review upon submission.
- ( ) Application for Exemption from IRB Review - Includes Exempt, Not Human Subject Research, & Not Research.
- ( ) External IRB Application - Any study using an external IRB as the IRB-of-Record.
- ( ) Trainee Research While Away from Duke - Research conducted by medical students overseen by the Office of Curriculum & other student/trainee research away from Duke.
- ( ) Individual Patient Expanded Access, Including Emergency Use - Use of an investigational product under expanded access, including emergency use of an investigational drug or biologic or emergency use of an unapproved device.

Conflict of Interest

Are any key personnel an inventor of any of the drugs, devices or technologies used in this research?

( ) Yes (●) No

Do any key personnel have a conflict of interest management plan issued by DOSI-COI related to this research?

( ) Yes (●) No

Oversight Organization Selection

CRU (Clinical Research Unit) or Oversight Organization Selection:

Please select the CRU.

Anesthesiology

The Clinical Research Unit that takes responsibility for this study.

- Please select **Medicine** as the CRU **only** if the PI is in one of these Divisions or Institutes: Endocrinology, Gastroenterology, General Internal Medicine, Geriatrics, Hematology, Infectious Diseases, Nephrology, Pulmonary, Rheumatology & Immunology, Center for Applied Genomics and Precision Medicine, Center for the Study of Aging and Human Development, Duke Molecular Physiology Institute.
- More information on CRUs can be found on the Duke Office of Clinical Research (DOCR) website, **http://docr.som.duke.edu**
- Questions concerning CRU selection should be directed to docr.help@dm.duke.edu.
- For questions about the Campus Oversight Organization, please visit **Campus Oversight Organization**.

List all Key Personnel on the study who are outside Duke:

- In the panel below, "PHI" is Protected Health Information.
- Note: If outside key personnel will have access to Duke PHI, you will need the following:
  - Attach the documentation of Human Subjects Certification for each individual, if they have completed the certification somewhere other than Duke.
  - A data transfer agreement AND external site IRB approval (or IRB authorization agreement). See HRPP policy **Use of Research Data by Former Duke Students or Former Duke Faculty and Employees**

Entry 1

Name	
Study Role	
Email Address	
Institution / Organization	
Will he/she have access to Duke P.H.I.?	○ Yes ○ No
Is he/she an unpaid volunteer at Duke on the study?	○ Yes ○ No

Describe Role of External Personnel:

Patients will receive care from their treatment team as they otherwise would were they not enrolled in the study. Patients will receive treatment from hyperbaric chamber personnel as they otherwise might were they not in this study.

Indicate the Protocol source below:

The protocol source is the author of the protocol. If the protocol is a joint authorship between multiple sources, select the primary author.

An IRB fee may be assessed for all research that is supported by for-profit entities and requires full board review. For additional information, see the **IRB fees section of the IRB web site**.

- ◉ Duke PI initiated
- ○ Commercial / Industry (for-profit entity) initiated
- ○ Federal Government initiated
- ○ Cooperative Group Initiated
- ○ Foundation (non-profit group) initiated
- ○ Other

Sponsor and Funding Source

Add all funding sources for this study: (Select 'Duke University' if you do not have funding or a sponsor for your study).

View Details	Sponsor Name	Sponsor Type	Contract Type:	Project Number	Award Number
⊟	Duke University	Institutional	Unfunded Research Collaboration		

Sponsor Name:	Duke University
Sponsor Type:	Institutional
Sponsor Role:	
Project Period:	From:09/06/2018 to:09/06/2020
Is Institution the Primary Grant Holder:	Yes
Contract Type:	Unfunded Research Collaboration
Project Number:	
Award Number:	

Grant Title:	
PI Name: (If PI is not the same as identified on the study.)	
Explain Any Significant Discrepancy:	

Is this a federally funded study?

○ Yes ◉ No

Does this study have any of the following?

- Industry sponsored protocol
- Industry funded Duke protocol
- Industry funded sub-contract from another institution
- Industry provided drug/device/biologic
- SBIR/STTR funded protocol

○ Yes ◉ No

As part of this study, will any samples or PHI be transferred to/from Duke to/from anyone other than the Sponsor, a Sponsor subcontractor, or a Funding Source?

○ Yes ◉ No

Is the Department of Defense (DOD) a funding source?

○ Yes ◉ No

Mobile Devices and Software

Does this study involve the use of a software or a mobile application?

○ Yes ◉ No

List all software, including third party (non-Duke) and mobile apps, that will be utilized for ascertainment, recruitment, or conduct of the research/project: (eg, MaestroCare, DEDUCE):

This project will use Maestrocare, redcap, and the Duke research sites such as iris, oncore for compliance purposes.

Multi-site Research

Is this a multi-site study?

○ Yes ◉ No

Complete for each site if Duke is the Primary grant awardee or coordinating center:

Entry 1

Site Name:	
City:	
State/Province:	
Country:	
	Site Contact Information
Primary Contact Name:	
Primary Contact Phone:	
Primary Contact Email:	
	Site Details
Does the site have an IRB?	○ Yes ○ No
Site IRB approval expiration date:	
If date not provided, explanation of why:	
Has the site granted permission for the research to be conducted?	○ Yes ○ No
Does the site plan to rely on the DUHS IRB for review?	○ Yes ○ No
What is the status of the study at this site?	○ Open ○ Closed
Site approval letters or site personnel lists:	Attach site approval letters, site closure letters (if applicable), or site personnel lists in the Initial Submission Packet.

Research Abstract

Please type your Research Abstract here:

The Research Abstract should summarize the main points of your study in one paragraph. The following guidelines may help you:

1. Purpose and objective (1-2 sentences)
2. Study activities and population group (2-4 sentences)
3. Data analysis and risk/safety issues (1-2 sentences)

We are proposing a clinical study to test the hypothesis that Hyperbaric Oxygen (HBO_2) given in the immediate postoperative period for a total of 10 treatments after Below-the-Knee Amputation (BKA) will reduce postoperative complications. Patients scheduled for BKA at Duke University Medical Center will be reviewed for contraindications to HBO_2. Patients for whom HBO_2 is not contraindicated may choose to be enrolled in the study. Patients enrolled will be randomly assigned to receive treatment or standard postoperative care. Each patient receiving treatment will receive twice daily HBO_2 for 2 hours at 2 ATA. Patients receiving HBO_2 will breathe 100% oxygen via head tent while inside a hyperbaric chamber at Duke University Hospital. The statistical plan for this study will test non-directional hypotheses (two-sided tests). Bonferroni correction will be used to adjust for multiple tests. SAS 9.4 (SAS Institute, Inc.) will be used to analyze the data. The main analysis of the primary efficacy hypotheses will include data from all randomized patients in the group to which random assignment is made. Hence, the analysis will be intention to treat.

Research Summary

State your primary study objectives

This study will primarily aim to assess whether patients receving treatment suffered fewer complications, as defined by the Vascular Quality Initiative, vs. patients who receive standard care.

State your secondary study objectives

This study will secondarily collect data pertaining to hospital length of stay, 90-day mortality, failure to heal at 4 and 8 week follow-up visits and ability to ambulate with a prosthesis at 6 months post amputation.

Please select your research summary form:

Standard Research Summary Template

This is the regular (generic) research summary template which is required for all regular applications (unless your protocol fits under the other research summary templates in this category). Use of these instructions is helpful for ensuring that the research summary contains all necessary elements.

Standard Research Summary

Purpose of the Study

- Objectives & hypotheses to be tested

This study is being conducted to assess the utility of hyperbaric oxygen as an adjunctive treatment to reduce postoperative complications. It is hypothesized that HBO_2 given in the immediate postoperative period will reduce postoperative complications in patients undegoing below-the-knee amputations. The objective of this study will be to compare treatment and standard care groups, randomly created of eligible patients, to compare their postoperative complications and to assess their postoperative hospital length of stay, 90-day mortality, failure to heal at 4 and 8 week follow-up visits and ability to ambulate with a prosthesis at 6 months post amputation.

Background & Significance

- Should support the scientific aims of the research

Lower limb amputations (LLA) are commonly performed at Duke University Hospital and are associated with major morbidity, mortality, hospital length of stay and costs. We are proposing a clinical study to test whether hyperbaric oxygen therapy (HBO_2) administered immediately after surgery for ten 2 hour treatments following below knee amputation (BKA) in diabetic patients will reduce surgical site infections (SSIs), reoperations and hospital length of stay (LOS).

LLAs have major morbidity and mortality. Overall, more than 60% of patients who require LLA are diabetic[1]. Wound complications occur in 12%, and reoperations in 10-16%, often for infection[1,2]. Nearly 5% of BKAs require revision to a higher amputation level[2]. Duke University Vascular Quality Initiative (VQI) data indicates that of the 98 LLAs performed at Duke last year 27 resulted in complications, of which 25 needed reoperation. Surgical complications after amputations result in roughly doubling of the cost incurred by hospitals[3], thus less than one third of amputations incur almost half of the total cost of amputations.

Both wound healing[4] and infection risk[5] are related to the partial pressure of oxygen (PO_2), in affected tissues. Higher peri-wound PO_2 stimulates wound angiogenesis[6,7] and decreases infection rate[8]. In patients requiring LLA, decreased blood flow due to diabetic microvascular disease and large vessel disease contributes to tissue hypoxia. In this population the combination of hyperglycemia and low tissue PO_2 is the major reason for both poor wound healing and surgical site infection (SSI).

Hyperbaric oxygen (HBO_2) can increase wound PO_2 to supranormal levels even in the presence of peripheral vascular disease[9]. Evidence suggests that HBO_2 can facilitate healing in chronic diabetic foot ulcers[10,11]. A retrospective analysis suggests that perioperative HBO_2 may prevent postoperative neurosurgical infections[12]. Regarding postop SSIs and perioperative high inspired O_2, although there has been some inconsistency in the published data[13], well-executed studies have supported the notion that high-inspired O_2 during anesthesia may prevent SSIs[14,15]. Hyperbaric oxygen specifically has been shown to be effective in the treatment of sternal infection, a classic complication of a poorly perfused surgical wound, and osteomyelitis after cardiothoracic surgery[16]. A double blind placebo controlled trial has showed the efficacy of HBO_2 as an adjunct to managing crush injuries of the limbs[17].

Recently concern has been raised about some adverse consequences of perioperative hyperoxia, including increased respiratory complications and mortality[18]. However, a Cochrane systematic review from 2015 reported no statistically significant effect of intraoperative oxygen concentration on all-cause mortality[13]. H owever, possible beneficial effects of hyperoxia are likely to be minimal when the focus is on the intraoperative phase, when an anesthesia provider is continuously providing careful management of blood pressure, blood glucose and administering fluid therapy. We feel, and studies cited above have shown, that the greatest beneficial impact of hyperoxia is likely to be after surgery, when the processes of healing and host response to bacterial infection occur over several days or weeks. Hence, the proposed intervention is intended to maximize the demonstrated beneficial physiological effects of hyperoxia by inducing it in the postoperative period.

Citations:
1. Curran T, Zhang JQ, Lo RC, Fokkema M, McCallum JC, Buck DB, et al. Risk factors and indications for readmission after lower extremity amputation in the American College of Surgeons National Surgical Quality Improvement Program. J Vasc Surg. 2014;60(5):1315-24
2. Gabel J, Jabo B, Patel S, Kiang S, Bianchi C, Chiriano J, et al. Analysis of Patients Undergoing Major Lower Extremity Amputation in the Vascular Quality Initiative. Ann Vasc Surg. 2018;46:75-82.
3. Healy MA, Mullard AJ, Campbell DA, Jr., Dimick JB. Hospital and Payer Costs Associated With Surgical Complications. JAMA Surg. 2016;151(9):823-30.
4. Knighton DR, Silver IA, Hunt TK. Regulation of wound-healing angiogenesis-effect of oxygen gradients and inspired oxygen concentration. Surgery. 1981;90(2):262-70.
5. Allen DB, Maguire JJ, Mahdavian M, Wicke C, Marcocci L, Scheuenstuhl H, et al. Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms. Arch Surg. 1997;132(9):991-6.
6. Hopf HW, Gibson JJ, Angeles AP, Constant JS, Feng JJ, Rollins MD, et al. Hyperoxia and angiogenesis. Wound Repair Regen. 2005;13(6):558-64.
7. Sheikh AY, Rollins MD, Hopf HW, Hunt TK. Hyperoxia improves microvascular perfusion in a murine wound model. Wound Repair Regen. 2005;13(3):303-8.
8. Hopf HW, Hunt TK, West JM, Blomquist P, Goodson WH, 3rd, Jensen JA, et al. Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. Arch Surg. 1997;132(9):997-1004; discussion 5.
9. Fife CE, Buyukcakir C, Otto GH, Sheffield PJ, Warriner RA, Love TL, et al. The predictive value of transcutaneous oxygen tension measurement in diabetic lower extremity ulcers treated with hyperbaric oxygen therapy: a retrospective analysis of 1,144 patients. Wound Repair and Regeneration. 2002;10(4): 198-207.

10. Fife CE, Buyukcakir C, Otto G, Sheffield P, Love T, Warriner R, 3rd. Factors influencing the outcome of lower-extremity diabetic ulcers treated with hyperbaric oxygen therapy. Wound Repair Regen. 2007;15(3): 322-31.
11. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev. 2015
12. Inanmaz ME, Kose KC, Isik C, Atmaca H, Basar H. Can hyperbaric oxygen be used to prevent deep infections in neuro-muscular scoliosis surgery? BMC Surg. 2014;14:85.
13. Wetterslev J, Meyhoff CS, Jorgensen LN, Gluud C, Lindschou J, Rasmussen LS. The effects of high perioperative inspiratory oxygen fraction for adult surgical patients. Cochrane Database Syst Rev. 2015(6): CD008884.
14. Greif R, Akca O, Horn EP, Kurz A, Sessler DI. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. Outcomes Research Group. N Engl J Med. 2000;342(3):161-7.
15. Myles PS, Leslie K, Chan MT, Forbes A, Paech MJ, Peyton P, et al. Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial. Anesthesiology. 2007;107(2):221-31.
16. Yu W-K CY-W, Shie H-G, Lien T-C, Kao H-K, Wang J-H. . Hyperbaric oxygen therapy as an adjunctive treatment for sternal infection and osteomyelitis after sternotomy and cardiothoracic surgery. Journal of Cardiothoracic Surgery. 2011;6:141.
17. Alquier GBPCJPGJLTATP. Hyperbaric Oxygen Therapy in the Management of Crush Injuries: A Randomized Double-Blind Placebo-Controlled Clinical Trial. The Journal of Trauma: Injury, Infection, and Critical Care 1996;41(August):333-9.
18. Meyhoff CS, Jorgensen LN, Wetterslev J, Christensen KB, Rasmussen LS, Group PT. Increased long-term mortality after a high perioperative inspiratory oxygen fraction during abdominal surgery: follow-up of a randomized clinical trial. Anesth Analg. 2012;115(4):849-54.

Design & Procedures

- Describe the study, providing details regarding the study intervention (drug, device, physical procedures, manipulation of the subject or the subject's environment, etc.). Discuss justifications for placebo control, discontinuation or delay of standard therapies, and washout periods if applicable. Identify procedures, tests and interventions performed exclusively for research purposes or more frequently than standard of care. Include alternative therapies, concurrent therapies discontinued per protocol, risk benefit ratio, and use of tissue/specimens. Discuss monitoring during washout periods if applicable. Include brief description of follow-up, if any.

Patients will be recruited at Duke University Medical Center and reviewed for contraindications to HBO_2. These include bullous lung disease, chronic hypercapnia or hypoxemia, pregnancy, chronic middle ear disease that precludes equalization of middle ear pressure, recent therapy with bleomycin or mitomycin C and unwillingness to participate in HBO_2 treatments. Recruitment will consist of in person discussion with patients by study personnel.

After informed consent is obtained, patients will be assigned to either a treatment group or a standard care group. Because of the nature of the treatment blinding is not possible. Patients will be informed of their group assignement when they arrive on the floor after surgery. Each patient in the treatment group will receive HBO_2 treatments in the Duke Center for Hyperbaric Medicine and Environmental Physiology using normal treatment protocols already established and approved by DUHS for the administration of HBO_2. Treatments will be given twice per day until the patient is discharged or 10 treatments are given.

Treatments will consist of breathing 100% O_2 through a head tent while inside a hyperbaric chamber at 2 ATA for 2 hours. Hyperbaric chambers at Duke allow for the presence of nursing staff and emergency access into the chamber while treatment is ongoing. Patients will experience a 15 minute compression and 5 minute decompression phase.

The Vascular Quality Initiative (VQI) is a multicenter voluntary reporting system for outcomes related to vascular surgery. The primary outcome of this study, postoperative complications, will be those outcomes meeting the definition set out in the VQI data dictionary, the set of definitions for inclusion in the VQI databse. This allows for a standard definition of complications recognized by a majority of academic medical centers across the country.

Secondary outcomes will include: Hospital length of stay, 90-day mortality, failure to heal at 4 and 8 week follow-up visits and ability to ambulate with a prosthesis at 6 months post amputation.
Patients will be examined daily during their inpatient stay and then at 4 and 8 week follow-up visits once discharged from the hospital. Periwound transcutaneous oxygen presures will be taken prior to administration of HBO_2 and at the completion of 10 treamtents.

The statistical plan for this study will test non-directional hypotheses (two-sided tests). Bonferroni correction will be used to adjust for multiple tests. SAS 9.4 (SAS Institute, Inc.) will be used to analyze the data. The main analysis of the primary efficacy hypotheses will include data from all randomized patients in the group to which random assignment is made. Hence, the analysis will be intention to treat, and regardless of subsequent events and every effort will be made to continue to follow all patients that begin the study.

Proportions and differences in proportions in the difference complication rate requiring reoperation in 30 days will be estimated along with 95% confidence interval. The difference in reoperation rates will be examined using Z-test. The analysis is similar for secondary outcomes. Exploratory outcome of 90-day mortality in the two treatment groups will be determined using Kaplan-Meier techniques with log-rank test. The Cox proportional hazards model will be used to determine the predictors of survival. Model assumptions will be examined and goodness of fit of these models will be assessed.

Because studies of this type have not been conducted before an effect size is difficult to estimate. However, based treatment of diabetic foot ulcers with HBO2[1] it is hoped that an effect size of 0.62, or reduction of complications by 60% can be seen. 80% power will be acheived by randomizing 40 subjects into each of the treatment and standard care groups. Hence, 80 subjects will be needed for this study. Given the high volume of operations conducted at Duke this should be achievable in less than 3 years. Midpoint analysis may produce results even sooner than that.

1. Löndahl M, Katzman, P., Nilsson, A., & Hammarlund, C. . Hyperbaric Oxygen Therapy Facilitates Healing of Chronic Foot Ulcers in Patients With Diabetes. . Diabetes Care. 2010;33(5):998-1003.

Selection of Subjects

- List inclusion/exclusion criteria and how subjects will be identified.

The subject selection will be equitable and all relevant demographic groups will have access to study participation (per 45CFR46.111(a)(3), 21CFR56.111(a)(3)).

Inclusion Criteria

1. Patients over the age of 18
2. Able to Consent
3. Have been identified as having a non-traumatic indication for amputation surgery of lower limb
4. Be cleared and scheduled for surgery for below-knee amputation of lower limb at Duke University Hospital
5. Be able to receive HBO_2 therapy.

Exclusion Criteria

1. Unable to consent
2. Unable to receive hyperbaric oxygen
3. No longer need to receive surgery for amputation of lower limb
4. Patients with End Stage Renal Disease on dialysis
5. Patients with current renal failure as measured by creatinine levels vs baseline change of more than 1 mg/dL and for whom dialysis is expected to be required within the next month
6. Patients with Calciphylaxis
7. Patients with traumatic injuries that are the cause of the amputation
8. Patients with cancer being treated by chemotherapy, scheduled to be treated, or being treated or scheduled to be treated by radiation.
9. Patients with limb amputation secondary to ischemic complications from other operations.
10. Patients undergoing a revision or reoperation on prior below-knee amputation
11. Patients undergoing above-knee amputation after prior below-knee amputation

Subject Recruitment and Compensation

- Describe recruitment procedures, including who will introduce the study to potential subjects. Describe how you will ensure that subject selection is equitable and all relevant demographic groups have access

to study participation (per 45 CFR 46.111(a) (3)). Include information about approximately how many DUHS subjects will be recruited. If subjects are to be compensated, provide specific prorated amounts to be provided for expenses such as travel and/or lost wages, and/or for inducement to participate.

Subjects will be recruited at DUH. Surgeons will identify subjects and refer them to the study coordinator for enrollment. All subjects will receive their surgery at Duke University Hospital. Any patient meeting the criteria will be accepted for the study. All relevant demographic groups have access to study participation (per 45CFR46. 111(a)(3), 21CFR56.111(a)(3)).

Until this point the number of patients coming through the outpatient clinic for primary amputation is very limited. Rather, the majority of patients requiring below-knee amputation have been going directly to the ED and being admitted. In mid-November one of the KPs will be transitioning to a new position with the inpatient vascular team, which is expected to greatly increase the opportunity to find eligible patients and discuss the study with them. She plans to develop a system to have the Vascular Surgery census reviewed twice per week to identify patients who may be eligible for the study.

Consent Process

- Complete the consent section in the iRIS Submission Form.

Subject's Capacity to Give Legally Effective Consent

- If subjects who do not have the capacity to give legally effective consent are included, describe how diminished capacity will be assessed. Will a periodic reassessment occur? If so, when? Will the subject be consented if the decisional capacity improves?

Subjects not competent to give consent themselves will not be allowed to participate in the study. Subjects who are incapacitated during the course of their inpatient stay, eg from delirium, will not receive HBO_2 unless and until they are competent again as determined by the treatment team.

Study Interventions

- If not already presented in #4 above, describe study-related treatment or use of an investigational drug or biologic (with dosages), or device, or use of another form of intervention (i.e., either physical procedures or manipulation of the subject or the subject's environment) for research purposes.

See above.

Risk/Benefit Assessment

- Include a thorough description of how risks and discomforts will be minimized (per 45 CFR 46.111(a) (1 and 2)). Consider physical, psychological, legal, economic and social risks as applicable. If vulnerable populations are to be included (such as children, pregnant women, prisoners or cognitively impaired adults), what special precautions will be used to minimize risks to these subjects? Also identify what available alternatives the person has if he/she chooses not to participate in the study. Describe the possible benefits to the subject. What is the importance of the knowledge expected to result from the research?

Only study participants in the treatment group will incur the risks listed below:

Risks of High Pressure
Barotrauma: with compression there is occasional difficulty getting the air pressure in the ears, sinuses, teeth, lungs and intestines to equal the increasing pressure outside the body. Aural barotrauma, the most likely complication, is caused by incomplete pressure equalization between the middle ear and the external environment. This is caused by eustachian tube dysfunction and is accompanied by mild pain. Hearing loss, inflammation of the ear and sinusitis may occur. In most cases, these problems self-resolve within a few days. All subjects will be given standard hyperbaric chamber teaching about ear clearing and when to inform the chamber staff of ear pain during compression so that pressure equalization techniques (valsalva, sipping water, swallowing, yawning) can be attempted. Patients who have difficulty equalizing will be referred for otolaryngology consultation as per the hyperbaric medical service routine.

Occasionally individuals have air-filled cysts in their lungs. If such a person is exposed to increased pressure, the cyst could possibly rupture and cause the lung to collapse, requiring medical and/or surgical treatment. This complication is rare, and thus far has not occurred in this laboratory in greater than 20 years of experience involving thousands of patient exposures. Individuals with a history of bullous lung disease will not be excluded from study participation.

Risks of High Pressure Oxygen
Only study participants in the treatment group will incur the risks listed below:

Oxygen Toxicity: Exposure to higher-than-normal oxygen concentration can cause generalized shaking and even seizures. Oxygen induced convulsions are extremely uncommon at two atmospheres of pressure, however, if they were to occur they would be treated by removal of the oxygen head-tent by the chamber attendant which will cause the convulsion to cease. This is the routine procedure for this complication of hyperbaric oxygen. Single oxygen convulsions are not known to have neurological sequelae.

Visual Changes: Some patients undergoing repeat exposures to elevated oxygen pressure develop blurred vision at a distance after 20-30 exposures. This involves a change in the refractive index of the lens, which causes mild myopia. Vision usually normalizes in 2-3 months after treatment.

Costs to the Subject

- Describe and justify any costs that the subject will incur as a result of participation; ordinarily, subjects should not be expected to pay for research without receiving direct benefit.

There will be no medical costs to the subjects directly related to the study. Routine medical costs not associated with the study will remain the subject's responsibility.

Data Analysis & Statistical Considerations

- Describe endpoints and power calculations. Provide a detailed description of how study data will be analyzed, including statistical methods used, and how ineligible subjects will be handled and which subjects will be included for analysis. Include planned sample size justification. Provide estimated time to target accrual and accrual rate. Describe interim analysis including plans to stop accrual during monitoring. Phase I studies, include dose escalation schema and criteria for dose escalation with definition of MTD and DLT.

The statistical plan for this study will test non-directional hypotheses (two-sided tests). Bonferroni correction will be used to adjust for multiple tests. SAS 9.4 (SAS Institute, Inc.) will be used to analyze the data. The main analysis of the primary efficacy hypotheses will include data from all randomized patients in the group to which random assignment is made. Hence, the analysis will be intention to treat, and regardless of subsequent events and every effort will be made to continue to follow all patients that begin the study.
Proportions and differences in proportions in the difference complication rate requiring reoperation in 30 days will be estimated along with 95% confidence interval. The difference in reoperation rates will be examined using Z-test. The analysis is similar for secondary outcomes. Exploratory outcome of 90-day mortality in the two treatment groups will be determined using Kaplan-Meier techniques with log-rank test. The Cox proportional hazards model will be used to determine the predictors of survival. Model assumptions will be examined and goodness of fit of these models will be assessed.

Based on randomized control trials of HBO_2 effects on healing diabetic foot ulcers this study is proposed to achieve 80% power to detect an effect size of 0.62, or reduction of complications by 60% by randomizing 40 subjects into each of the treatment and placebo groups. Hence, 80 subjects will be needed for this study. Given the high volume of operations conducted at Duke this should be achievable in less than 3 years.

Data & Safety Monitoring

- Summarize safety concerns, and describe the methods to monitor research subjects and their data to ensure their safety, including who will monitor the data, and the frequency of such monitoring. If a data monitoring committee will be used, describe its operation, including stopping rules and frequency of review, and if it is independent of the sponsor (per 45 CFR 46.111(a) (6)).

Clinical and demographic data will be collected electronically and stored using Duke University's Redcap system. Information pertaining to blinding, patient treatment, or any other study information that may arise incidentally will be stored in the Duke hyperbaric treatment facility in a locked cabinet in the nurse manager's office.

Privacy, Data Storage & Confidentiality

- Complete the Privacy and Confidentiality section of the iRIS submission form.

Study Scope

Does this study have a cancer focus? Cancer focus includes studies that enroll >50% oncology or malignant hematology patients; or, preventing, detecting, and diagnosing cancer or understanding the impact of cancer on patients and their caretakers.

○ Yes ◉ No

Does this study involve the use of a drug, biologic, food, or dietary supplement?

◉ Yes ○ No

Does this study involve the use of a medical device, an algorithm (whether computer based or not), an in vitro diagnostic test, or samples to look for biomarkers?

○ Yes ◉ No

Does this study employ magnetic resonance, including imaging (MRI), spectroscopy (MRS), angiography (MRA) or elastography (MRE) beyond the standard of care?

○ Yes ◉ No

Does this study specify or require the performance of diagnostic procedures using ionizing radiation (x-rays, DEXA, CT scans, nuclear medicine scans, etc.) that are beyond the standard of care?

○ Yes ◉ No

Does this study specify or require the performance of therapeutic procedures using ionizing radiation

(accelerator, brachytherapy or systemic radionuclide therapy) that are beyond the standard of care?

○ Yes ◉ No

Does this study specify or require the use of a laser system for diagnosis or therapy that is beyond the standard of care (excludes the use of lasers as a standard surgical instrument)?

○ Yes ◉ No

Will the participant be subjected to increased or decreased ambient pressure?

◉ Yes ○ No

Please justify the reasons for the exposure and the safety of doing so by describing the safety measures.

The study is to determine specifically whether subjects benefit from hyperbaric oxygen. Administration of hyperbaric oxygen requires exposure to higher than ambient pressure. The Duke Center for Hyperbaric Medicine and Enviornmental Physiology houses Duke University Hospital's treatment chambers where patients will receive their treatments. Safety procedures are strictly followed at Duke and the chamber's record of safety is excellent. The chamber's at Duke are the only civilian chambers in the world to be certified by the U.S. Navy.

Do you plan to recruit subjects from Duke Regional Hospital (DRH)?

○ Yes ◉ No

Do you plan to recruit subjects from Duke Raleigh Hospital (DRAH)?

○ Yes ◉ No

Does this study include using the Duke logo in any advertisements?

○ Yes ◉ No

Is this study retrospective, prospective, or both?

"Retrospective" means that data or samples already in existence (collected prior to the study submission) will be used.
"Prospective" means there will be data or samples collected in this study for research purposes.

○ Retrospective
◉ Prospective
○ Retrospective and Prospective

If the study is both retrospective and prospective: Is this a review solely of information collected for non-research purposes (i.e. a review of medical records)?

○ Yes ○ No

Does this protocol include any research using botulinum toxin, including the FDA-approved clinical product (Botox)?

○ Yes ◉ No

Does this protocol involve the administration of any of the following materials to humans?

- Any viral vector or plasmid
- Any cells that have been modified by a viral vector
- Any other genetically-modified cells
- Any genetically-modified virus, bacterium, or other agent
- Any other recombinant or synthetic nucleic acid

○ Yes ◉ No

Subject Population Groups and Enrollment

Population Groups (Select targeted population groups only):

- ☑ Adults
- ☐ Minors who are Wards of State
- ☐ Minors
- ☑ Duke Patients
- ☐ Pregnant individuals
- ☐ Fetuses
- ☐ Prisoners
- ☐ Adults incapable of giving consent
- ☐ Adults with diminished capacity
- ☐ Disabled subjects
- ☐ Students
- ☐ Employees
- ☐ Healthy Controls
- ☐ Deceased subjects
- ☐ Blanket Protocol

Please select any population groups excluded from participation in this study:

- ☑ Pregnant individuals

Will you administer a pregnancy test to eligible female subjects prior to the start of study activities?

◉ Yes ○ No

Maximum number of subjects to be consented at Duke:

Enter a single number. If you anticipate consenting a range of subjects, enter the **upper** limit of the range. The number should represent the maximum number of subjects for the life of the study.

140

Maximum number of subjects to be consented at all sites:

Enter a single number. If you anticipate consenting a range of subjects, enter the **upper** limit of the range. The number should represent the maximum number of subjects for the life of the study.

140

Subject Procedures and Costs

Biobank - Does this study involve the collection, use, tracking, banking (storage) or distribution of human biological specimens?

Human biological specimens include blood or its components, healthy or diseased tissue, bodily fluids, DNA /RNA or human stem cells.

○ Yes ◉ No

Procedures

Check all that apply:

- ☐ Genetic Testing
- ☐ Gene Transfer
- ☐ DNA Banking
- ☐ Testing for Reportable Infectious Diseases
- ☐ Human Cell Banking
- ☐ *Use of Human Embryonic Stem Cells
- ☐ *Use of Human-induced Pluripotent Stem Cells
- ☐ *Use of Other Cells Derived from Human Embryos
- ☐ *Use of Human/Animal Chimeric Cells
- ☐ *Specialized Cell Populations for Cell Therapy
- ☐ Use of Human Tissue
- ☐ Use of Bodily Fluids
- ☐ Use of Blood (or its components)
- ☑ Not Applicable

Will blood be drawn in this study for research purposes?

○ Yes ◉ No

Will the Operating Room be used in this study?

Include only research time, not clinical care time.

○ Yes ◉ No

Will there be extra costs to subjects or insurance as a result of the research (e.g. tests, hospitalization)?

○ Yes ◉ No

Will there be Subject Compensation?

○ Yes ◉ No

Subject Recruitment Materials

For each document to be reviewed, use the table below to provide the following information:

Attach a copy of each advertisement to be used with this study in the Initial Submission Packet. If any Advertisement will have multiple wording variations, attach a copy of each version of the Advertisement.
The IRB must approve all study advertisements used to recruit subjects.

Types of subject recruitment materials include, but are not limited to, the following:

Direct Advertising
Posters
Billboards
Flyers
Brochures

Media Advertising
Newspaper Ads
Magazine Ads
Radio Ads
TV commericals / Video
Internet website
Social Media

Other Types of Advertising
Newsletter
Email
Postcards / Letters

(Note: Doctor-to-Doctor letters do not require IRB approval)

Document name	Material category	Location material displayed	Has this material previously been approved by the IRB?
No records have been added			

Consent Process

Attach draft consent forms in the Initial Review Submission Packet.

Consent forms must be MS Word documents and follow the specific format outlined by the IRB. **Click here** to download a copy of the consent form template.

Note: Please do not edit the section of the footer that contains the Protocol ID, Continuing Review and Reference Date fields. Those fields will be used to stamp the final consent form when it is approved by the IRB. If you want to add an internal version date, please put it in the header.

Who will conduct the consent process with prospective participants?

Provide their role(s) in this study (PI, Study Coordinator, etc.):

The consent process will either be conducted by the PI, any Co-I's, or the study coordinator.

Who will provide consent or permission?

(Select all that apply):

- [x] Participant
- [ ] Parent(s) or Legal Guardian(s)
- [ ] Legally Authorized Representative (LAR)

How much time will the prospective participant (or legally authorized representative) have between being approached about participating in the study and needing to decide whether or not to participate?

If you are not giving the person overnight to consider whether or not to participate, please justify.

Subjects will have as much time as possible to consider their participation and may withdraw at any time. Since they will be approached at pre-surgical appointments and can conset any time up until their date of surgery patients should have days to weeks to consider their participation.

Where will the consent process occur?

Patients will be offer the opportunity to consent in their pre-surgical appointments. They may also consent on the day of surgery or any day up until that day by contacting the clinical coordinator.

What steps will be taken in that location to protect the privacy of the prospective participant?

Consent will be given in clinical care areas of Duke (i.e. in exam rooms) and so privacy should be protected along with and at the same level as all other clinical care.

How much time will be allocated for conducting the initial consent discussion, including presenting the information in the consent document and answering questions, with each prospective participant?

Patients will have as long as they desire to discuss their participation and will then be able to follow up in writing or by phone with the clinical coordinator. Approximately 20-30 minutes will be allocated in addiion to their regular appointments. The clinical coordinator will be available for follow up by phone or email.

What arrangements will be in place for answering participant questions before and after the consent is signed?

The attending surgeon and clinical coordinator will be available during the initial approach of the subjects for consent. The clinical coordinator will be available by phone or email to follow up with patients to answer questions. The Duke Center for Hyperbaric Medicine and Environmental Physiology is accessable to patients by appointment and patients may choose to visit the facility prior to their surgery to see the chambers and meet chamber staff.

Describe the steps taken to minimize the possibility of coercion or undue influence.

No compensation will be given to patients for this study. There is no incentive for patients to enter into the study beyond the possibiity that they may receive and benefit from HBO_2.

As much as possible all care is standardized from one patient to the next such that the only difference in care received by patients is that which is medically necessary for individual conditions. Hence, there is no benefit or loss for patients whether they are in the study or not.

Patients will be consented as early as possible so that patients have the longest time between entering into the study and the beginning of treatment to consider their involvement. Since patients may withdraw from the study at any time, this should limit any time pressure or other situational influence that may arise during the initial consent process.

What provisions will be in place to obtain consent from participants who do not read, are blind or who do not read/understand English?

Patients who are not able to read the consent form themselves will be offered translation services, sign interpretation, or other helpful adaptive services to facilitate communication of information about the study and the consent process to them. Blind or non-reading patients may choose to have the consent read aloud. In no case will study subjects be allowed to have consent given for them. Each participant must be able to consent for themselves so every effort will be made to provide all information needed for consent to patients directly.

Do you plan to obtain written consent for the conduct of research?

(•) Yes ( ) No

Protected Health Information (PHI)

Indicate how you intend to use potential subjects' Protected Health Information (PHI):

(•) I will review, but not record, PHI prior to consent.
( ) I will record PHI prior to consent.
( ) I do not intend to use PHI prior to consent.
( ) I will record PHI without consent. (decedent research, database repository, chart review)

Review Preparatory to Research (RPR)

Describe the specific PHI that will be reviewed to prepare a research protocol and/or to ascertain and/or recruit subjects:

Patient PHI may be reviewed to determine eligibility prior to their consent for the study. This will occur in conjunction with their normal preoperative care.

Principal Investigator's Affirmation:

The PHI is necessary for the purposes of this activity.

(•) Yes ( ) No

The PHI will be used solely for this activity.

(•) Yes ( ) No

The PHI will not leave DUHS.

(•) Yes ( ) No

The PHI will not be written down or recorded prior to the subject signing a research consent form.

(•) Yes ( ) No

I will not use the information accessed through this RPR procedure for any other purpose, including for presentation or publication.

(•) Yes ( ) No

Drugs, Biologics, and Other Substances

Select Protocol Phase (for studies with FDA regulated drugs or biologics only). Choose only one:

( ) Phase 0
( ) Phase I
( ) Phase I/II
(•) Phase II
( ) Phase II/III
( ) Phase III
( ) Phase IV
( ) N/A
( ) Pilot

Drugs, biologics, or other substances being evaluated as a part of this research study:

Add all drugs, biologics, or other substances being evaluated as a part of this research study for which an IND is provided for the indication used in this study.
Also add any other drugs, biologics or other substances here that are being used as a part of this research study, for which an IND is not provided.

List every other drug, biologic or other substance for which side effects are described in the consent form.

View Details	Drug Name	FDA Approved	A new drug or a new use of approved drug:	IND Number
⊟	**Drug/Biologic/Substance Generic Name:** Hyperbaric oxygen **Generic Drug Name:** **Investigational Drug Name:**	Yes	No	

Drug/Biologic/Substance Generic Name:	Hyperbaric oxygen
Generic Drug Name:	
Investigational Drug Name:	
Drug/Biologic/Substance Source:	
Is the drug/substance being provided to the subject free-of-charge?	Yes
Is the Drug FDA Approved?:	Yes
Is this drug/biologic or other chemical, metabolite, nutritional substance or other substance to be used in this research subject to the provisions of the Controlled Substances Act?	No
Does this Drug have an IND Number?	No
IND Number	
IND Holder:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	Medical grade oxygen is used for this study.
Will drug/substance be shipped from Duke to external locations	No
Dose Range:	2 ATA/2 hours
Frequency:	2x daily
Will this drug, biologic, chemical, metabolite, nutritional substance or other substance be manufactured or compounded at Duke?	No
Drug Storage Restrictions (including temperature, etc.):	N/A
As indicated in the Investigator's Brochure or other available	

documentation, what is the highest FDA Use-in-Pregnancy Rating for drug used for research purposes in this study?:	N/A

Are you using an investigational pharmacy at Duke?

Please be aware that inpatient administration of an investigational drug requires the use of the Duke IDS or Oncology ICS, as per Department of Pharmacy policy.

○ Yes ◉ No

Who will be responsible for the storage, inventory and control of the drug/biologic or other chemical, metabolite, nutritional substance or other substance to be evaluated in this research?

The IDS is available to assist any investigator (upon request) with storage and control of investigational drugs in the outpatient setting

The oxygen to be used in this study is standard medical grade oxygen, from the same source as all Duke patients receive (see uploaded document).

Where will the drug/biologic or other chemical, metabolite, nutritional substance, or other substance to be evaluated in this research be stored?

N/A

From where will the drug/biologic or other chemical, metabolite, nutritional substance or other substance to be evaluated in this research be dispensed?

Duke Center for Hyperbaric Medicine & Environmental Physiology

At the completion of this research study, what will be done with the unused or returned investigational drug /biologic or other chemical, metabolite, nutritional substance or other substance?

N/A

Privacy and Confidentiality

Explain how you will ensure that the subject's privacy will be protected:

Consider privacy interests regarding time and place where subjects provide information, the nature of the information they provide, and the type of experience they will be asked to participate in during the research.

All information will be protected and PHI will be handled in accordance with all DUke policies and procedures. Redcap will be used for data collection and storage and primary documents will be stored in the study binder kept in a locked cabinet in the Duke Hyperbaric lab. Patients will be consented and have the ability to ask questions in patient care areas where curtains, exam rooms, and other strategieis for protecting patient confidentiality will be used to protect patient privacy.

Describe how research data will be stored and secured to ensure confidentiality:

How will the research records and data be protected against inappropriate use or disclosure, or malicious or accidental loss or destruction? Records and data include, for example, informed consent documents, case report forms or study flow sheets, survey instruments, database or spreadsheets, screening logs or telephone eligibility sheets, web based information gathering tools, audio/video/photo recordings of subjects, labeled specimens, data about subjects, and subject identifiers such as social security number.

Data will be stored using the Duke redcap system. Primary data that is in paper form will be stored in the study binder kept in a locked cabinet. All correspondence regarding the program will occur through the Duke email system.

Application Questions Complete

Please click Save & Continue to proceed to the Initial Submission Packet.

The Initial Submission Packet is a short form filled out after the protocol application has been completed. This is an area to attach protocol-related documents, consent forms, and review the application.