PROPOSAL FOR HUMAN RESEARCH

CLINICAL INVESTIGATION FACILITY
60th Medical Group (AMC)
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APPROVED
INP KVW
MAR 12 2019

60 MDG IRB
TRAVIS AFB CA

FWA00003321, DoD 50004, IRB00011217

For assistance, call the Chief, Research Oversight and Compliance at (707) 423-7206

1. Title of Investigation

The Effects of Hyperbaric Oxygen on Rheumatoid Arthritis: a Pilot Study.

2. Investigator and Investigation Staff

Name	Rank	Study Role	Date of Investigator Training	Staff/ Resident/ Fellow	Dept/ Office Symbol	Phone	DoD Assurance Number	E-mail
	Lt Col	PI	12/8/17	Staff	SGOM		50004	
names redacted	CTR	AI	1/22/18	Staff	SGPH		50004	
28 Jan 20	Lt Col	AI	9/28/17	Staff	SGPH			
	Maj	AI	1/5/18	Staff	SGQX		50004	contact inf o redacted 28 Jan 20
		Consultant	12/4/17	Volunteer				
	Maj	RM	7/19/17	Staff	SGSE		50004	
	CTR	CRC	4/10/18	Staff	SGSE		50004	
	CTR	CRN	6/19/17	Staff	SGSE		50004	
	CTR	RA	8/5/17	Staff	SGSE		50004	

name redacted 28 Jan 20	CTR	CRC	2/4/19	Staff	SGSE		50004	**contact inf o redacted 28 Jan 20**

Research Monitor (RM): name redacted 28 Jan 20, 60 MDG/SGSE

3. Facility and/or Contractor: N/A

4. Purpose of Investigation

This is a pilot study. The purpose of this investigation is to determine the effects and feasibility of using hyperbaric oxygen therapy (HBO2) for the treatment of rheumatoid arthritis joint pain and prevention of disease progression. In this study it is our intention to not only evaluate effects and feasibility but time, cost, adverse events and effect size in an attempt to predict an appropriate sample size and improve on the study design prior to a more extensive study.

5. Category of Study and Risk Assessment

5.1. Category of Study

Pilot Study. Hyperbaric oxygen is not an established treatment for rheumatoid arthritis.

☐ **Medical Utilization** ☐ **Prevention** ☐ **Medical Readiness** ☒ **Diagnosis/Treatment/Other**

5.2. Proposed Risk:

☐ Minimal Risk
☒ Greater Than Minimal Risk

6. Proposed Research

6.1. Background and Review of Literature:

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder of unknown etiology that primarily involves synovial joints, typically symmetrically. If untreated and/or uncontrolled, joint destruction due to erosion of cartilage and bone can cause joint destruction, joint deformities, loss of physical function, severe disability, and difficulties maintaining employment.[1] ACR/EULAR 2010 classification criteria[2] is a score-based algorithm which adds scores of four categories including, joint involvement, serology, acute-phase reactants and duration of symptoms. A score of >6/10 is needed for classification of a patient as having definite RA.

Non-pharmacologic and supplementary therapies include patient education, rest, exercise, nutrition counseling, cardiovascular disease risk reduction, and immunizations to decrease risk of infectious complications of immunosuppression. These are important in the comprehensive management of RA in all stages of disease and are used in addition to drug therapy. Pharmacologic therapies typically start with a disease-modifying antirheumatic drug (DMARD), preferably as soon as possible after diagnosis. DMARDs are commonly used in combination with anti-inflammatory drugs such as nonsteroidal anti-inflammatory

drugs (NSAIDs) and glucocorticoids which are often used as bridging therapies until the DMARDs become effective. The goal is disease remission. To assess response, disease activity scores are used along with inflammatory markers[3]

David Grant USAF Medical Center Case Experience

Three patients with active RA treated in the multi-place hyperbaric facility at DGMC, Travis Air Force Base, CA, for non RA-related indications, all noted significant improvement in arthralgia's, sleep patterns and overall well-being during the course of therapy. Two were treated at two atmospheres absolute (ATA) oxygen for 90 minutes daily Monday through Friday. One patient received two ATA air on the same treatment protocol as a participant in a research study, and a subsequent course of hyperbaric oxygen (HBO2) at two ATA.

Sixty-two year old female with diabetes, hypertension (HTN), RA, status post double mastectomy referred for HBO2 for healing enhancement of infected and poorly healing bilateral surgical sites. Immuno-suppressive medications were discontinued due to negative effect on healing. The patient had significant improvement of joint pain early in her course of HBO2 (< 10 sessions). She received a total of 55 treatments, last 17 Dec 2014. She had no RA pain recurrence for 13 months after the last HBO2 session. After complete healing of the mastectomy sites was assured, RA meds were restarted.

Seventy-one year old male with diabetes mellitus (DM), RA, treated with 50 HBO2 sessions ending in May 2013 for chronic, non-healing foot ulcers. A second course of therapy for the same diagnosis ended in May 2015 (31 sessions). Arthralgias slowly returned after about six months following the first course of HBO2, and still has significant clinical benefit six months after the last course of HBO2. Both times, the patient experienced not only complete relief of his arthralgias within the first seven daily (five days/week) HBO2 sessions, but also had significant clinical improvement in his chronic, bilateral Dupuytren's contractures.

Fifty-nine year old male with DM and RA, was a subject in a double-blind, randomized research study on the use of HBO2 in patients with Wagner 2 diabetic wounds in the fall of 2014. When the study was discontinued, it was determined that the patient had been randomized to the control group and received 30 sessions of hyperbaric air at 2 ATA per research protocol. During the study participation, the patient had complete relief of his chronic joint pain due to rheumatoid arthritis within one to two weeks of the study participation period, without a change in his medications. He also noted significant improvement in sleeping patterns. About one month after ending the research study hyperbaric exposures, the patient had a significant RA flair. He was seen several times in the ER for worsening RA pain. He was disenrolled for follow-up in the research trial in Feb 2015 so that he could be treated with HBO2 for the RA flare, and for an infection and healing enhancement of a right olecranon surgical site. The patient again had complete relief of arthralgias within three to four HBO2 sessions, was able to sleep through the night and able to significantly increase his activity level.

It seems intuitively unlikely that the latter a patient could benefit from both hyperbaric air and hyperbaric oxygen. The bioactivity of hyperbaric oxygen is well known. Although

lesser known, the bioactivity of increased atmospheric pressure is well documented in basic science literature. Independent and overlapping genes are sensitive to increases in pressure, oxygen, or both, and could explain the relief of pain from both hyperbaric air and oxygen.[4]

Literature Review

There is a paucity of information about the effects of HBO2 on patients with RA in the medical literature. A 1988 letter to the editor in the British Journal of Rheumatology reported ten patients with active classic or definite RA. Eight patients received ten HBO2 treatments at 2 ATA X 90 minutes on alternate days over a 21-day period. Two patients received 'sham' treatment breathing air at normal atmospheric pressure. Clinical assessments were made at -1, 0, 3 (end of treatment period), six and 12 weeks, and included duration of morning stiffness, grip strength, articular index and visual analogue pain scale. Lab indices included hemoglobin, platelet count and ESR. Rheumatoid factor (RF) was measured at times zero, three, and six weeks. The two pre-treatment assessments defined the range for each individual, and subsequent assessments were recorded as improved (+1), in range (0), or worse (-1). The authors concluded that there was a trend toward improvement in HBO2-treated patients. They concluded that the improvement was to be expected if active RA patients are recruited, and noted a similar trend in the sham-treated group. No patients went into remission, and the Rheumatoid Factor did not significantly change. The authors felt that their pilot study failed to demonstrate any therapeutic advantage of HBO2, and further trials were not justified. Weaknesses in this pilot study include small numbers of patients, likely sub-optimal course, frequency of HBO2 therapy and lack of utility of RF to measure disease activity. Larger differences in outcomes between the active and sham groups might have been realized if there were more patients enrolled for a longer, daily treatment course, and a more robust data analysis.[5]

In a 1990 abstract authors reported on their experience treating 50 RA patients with 12 sessions of HBO2 at 1.7 ATA for 40 minutes. All patients had been previously treated with prolonged traditional drug therapy with minor success. The authors reported good immediate and remote clinical results, the best, in patients with systemic manifestations. After HBO2, there were no changes reported in humoral immunity (IgA, IgM or IgG), but serum immune complexes decreased significantly, absolute and relative quantities of T- and B-lymphocytes approached normal levels, and the ratio of theophylline-resistant to theophylline-sensitive lymphocytes deceased significantly. The authors concluded that the beneficial effects of HBO2 on the immune system of the patients was related to intensification of the suppressive function of T-lymphocytes, normalization of cell-bound immunity and decreasing the serum concentration of immune complexes.[6]

A 2002 Russian article reported on 46 patients with rheumatoid arthritis (RA) and 18 with osteoarthritis (OA), all treated with 3.6-4 cGy radiotherapy (RT). Twenty-four of the RA, and ten of the OA patients were treated with a combination of oxygen barotherapy (OBT) consisting of 9-11 sessions at 1.4 bar (1.45 atmospheres absolute) for 40 minutes each, and RT to allow for optimal results from this complex therapy while reducing the known adverse effects of radiation. In the two years that followed, basic clinical assessments included the Ritchie articular index, total pain index, local articular index, pain index for knee and hand joints, circumference of knee and wrist joints, and ultrasound

measuring the magnitude of exudate, erosive processes, osteophytes, articular fissure stenosis, and the thickness of the synovial membrane and cartilage.

Joints irradiation after the oxygen barotherapy (OBT) session was associated with a more pronounced positive effect than RT alone, including significant positive findings in the Ritchie articular index, general pain index, and pain index of the knee joints.
For RA patients, ultrasonic investigations of knee joints revealed negative correlations between treatment effectiveness and synovial membrane thickness ($r= -0.65$, $p< 0.01$), and severity of effusion ($r= -0.71$, $p< 0.01$) for RA patients. For group three OA patients, there was no evidence of cartilage thinning throughout the observation period; progression was found in group 4 ($r= -0.83$, $p< 0.01$). Therapies for all groups were more effective in the early stages of the disease and the best outcomes were found in OA patients.[7]
Although this study evaluated the combination of OBT with radiation therapy for RA and OA patients, and found statistically significant improvement in indices of pain and disease progression, it raises the question of whether there is potential benefit from the use of OBT (hyperbaric oxygen) alone. This is especially true since OBT was at only the equivalent of 1.45 ATA for a total of 9-11 sessions, considering that most OBT sessions in the US are provided at 2 to 2.5 ATA, typically for more than ten sessions.

6.2. Relevance/Significance:

If hyperbaric oxygen consistently relieved the joint pain and stiffness associated with RA, led to an increase in exercise tolerance, activity level and sleep quality, and modified disease progression, there could be a significant role for the use of HBO2 as an adjunct to current therapies, and could reduce the amount of DMARD or Biologic therapy. This would be especially true for patients targeted as possible study participants: 1) those that prefer not to be on the standard rheumatologic medications, 2) those with contraindications to the standard rheumatologic medications, and 3) those that have failed or have incomplete response to standard rheumatologic medications.

6.3. Hypotheses or Research Questions or Objectives:

Proposed primary outcomes:

1. Subjective relief of joint pain, stiffness, and increased activity levels as assessed by the study rheumatologist as measured by disease activity monitoring score (DAS28)[8] and ACR20 criteria.
2. Improved sleep quality to be tracked separately by a sleep quality questionnaire.
3. Subjective improvement in movement and activities of daily living using the RAPID 3.
4. Visual Analog Scale (VAS)[10] for pain to assess changes in subjective pain.
5. Altering the progression of joint disease as measured by ultrasound and MRI measured at baseline, three months, six months.
6. Changes in inflammatory markers as measured by C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) to be performed at baseline, during HBO2 treatments if subject reports pain relief (defined as improvement of pain of > 40% or zero pain) based on pain assessment (numerical pain scale of 1-10 reported verbally) at

each hyperbaric treatment visit, at the completion of HBO2 treatments, at three months and six months.

A research lab sample for analysis of Microparticles, neutrophil and platelet activation [11] will be collected with each CRP/ESR. Microparticles represent a heterogeneous population of vescicles with a diameter of 100 to 1000 nm that are released by budding of the plasma membrane and express antigens specific to their parental cells. Although microparticle formation represents a physiological phenomenon, a multitude of pathologies are associated with a considerable increase in circulating miroparticles, including inflammatory and autoimmune diseases, atherosclerosis and malignancies.

6.4. Research Design and Methods:

HBO2 can be administered either in the multiplace chamber, or the monoplace chamber. The multiplace chamber is compressed with air, and the patients breathe oxygen through hoods or masks. The monoplace chamber is pressurized with oxygen, so that the patient breathes the ambient oxygen. Only the delivery system is different. There is no difference in the oxygen delivered, or in attendant risks.

This is a pilot study.

1. Patient eligibility will be determined by the Rheumatologists, specialists in diagnosing rheumatoid arthritis. Recruitment will take place from their pool of patients. Additionally, patients that have been seen in the military treatment facility (MTF) within the past year with a diagnosis of rheumatoid arthritis will be contacted, after obtaining IRB-approval with a HIPAA waiver. Patients will be recruited if they: diagnosed with rheumatoid arthritis meeting ACR/EULAR 2010 classification criteria and any one of the following:
    a. Patient does not want to be on rheumatologic medications.
    b. Patient has contraindications to standard rheumatologic medications.
    c. Patient has failed treatment or an incomplete response with standard rheumatologic medications.
2. The initial screening visit after the rheumatologist has discussed the trial will be the consenting and review of the inclusion/exclusion criteria. After the consent is signed the Hyperbaric physician will do a physical examination, review of inclusion and exclusion criteria and medication review to determine if it is safe for the subject to receive HBO2. An HCG by point of care testing (POCT) will be completed by the coordinator in women capable of pregnancy. After this exam is done the subject will be scheduled for a trial hyperbaric session.
3. The visit window timeline for screening, Baseline, and first HBO2 treatment to occur all within one month (four weeks) before start of HBO Hyperbaric Therapy Session.
4. **Baseline** The Baseline date is dive #1 date. This visit includes:
    - A visit with the rhematologist to do routine assessments to establish baseline measurement using the the Disease Activity Scale (DAS28)
    - Labs (CRP and ESR, Basic Metabolic Panel (BMP) and Microparticles) will be done. A MRI with and without contrast and ultrasound will be done on both hands

from wrists to proximal phalanges. BMP is done pre-MRI to guarantee adequate kidney function.

- Subjective patient reporting will be captured using the RAPID 3.
- Sleep quality will be tracked using the Pain and Sleep Quality Questionnaire (PSQ-3)[12].
- Visual Analog Score for Pain (VAS) will be tracked.
- Surveys will be administered by a study team member.

5. The subject at this time will be scheduled to start HBO2 treatments. Screening, baseline , first HBO2 treatment all in one month.
6. **During the period that the HBO2 treatments** are taking place the hyperbaric physicians will continue to monitor the subjects and if there is any concern regarding their physical condition they will consult with one of the rheumatologists. Participants will complete 30 sessions within 10 weeks.
7. If the subject reports pain relief, as defined as improvement of pain of > 40% or zero pain, during the HBO2 treatments they will be referred to the rheumatologist for assessment. Pain improvement will be based on a pain assessment (numerical pain scale of 1-10 reported verbally) at hyperbaric treatment visits. Labs (CPR, ESR and Microparticles) will be drawn at this time. RAPID 3 and PSQ-3 and VAS will be done at least six times while undergoing hyperbaric treatments to track subject progress. Labs (CRP, ESR and Microparticles) will be repeated at the conclusion of the HBO2 treatments.

8. At the **month three visit** (+/- 2 window) the subject will see the rheumatologist to track disease activity using the DAS-28. The date of the three month visit will be scheduled for three months from the Baseline visit. The Rheumatologist will order the MRI Ultrasound, and lab studies prior to the three month visit. RAPID 3, PSQ-3and VAS for pain will be administered at this time. Laboratory samples will be collected prior to the Rheumatology appointment.

9. At the **month six visit** (+/- 2 week window) the subject will see the rheumatologist to track disease activity using the DAS-28. The date of the six month visit will be scheduled for six months from the baseline visit. The Rheumatologist will order the MRI, Ultrasound, and lab studies prior to the six month visit. RAPID 3, PSQ-3 and VAS for pain will be administered at this time. Laboratory samples will be collected prior to the Rheumatology appointment.
This marks the end of the trial. Patients will continue to be followed in the Rheumatology Clinic every three months.

Study Visits

	Screening Visit (maybe split into 2 visits) ***	**Base line Visit** ***	**HBO TX** ***	**Pain relief during HBOT**	**Compl etion of HBOT**	**Mo 3** (+/- 2 weeks)	**Mo 6** (+/- 2 weeks)

ICD/ HIPAA	x						
Inclusion/ Exclusion Criteria	x						
Exam by Hyperbaric Physican	x						
Trial HBOT	x						
Hyperbaric treatments			X 30 * **				
Rheumatology Visit		x		x		x	x
Labs		x		x	x	x	x
Ultrasound		x				x	x
MRI		x				x	x
DAS 28		x		x		x	x
RAPID 3		X	x ****	x		x	x
PSQ 3		X	x ****	x		x	x
VAS Pain		x	x ▪▪▪▪▪▪▪	x		x	x

*When subject reports pain relief during HBOT they will be assessed by Rheumatologist.

** Complete 30 HBO treatments within 10 weeks.

*** Screening, Baseline, First HBOT treatment all within one month (four weeks)

**** at least 6 times while undergoing hyperbaric treatments

The optimal dose response of RA patients to HBO2 is unknown. Modest benefit has been shown in prior studies at 2 ATA and 1.5 bar for 10 and 9-11 sessions, respectively. The subject will be compressed with air in the hyperbaric chamber to 2.0 ATA, and then placed on 100% oxygen by a head tent or mask, for 90 minutes. After hood removal, the chamber is decompressed while the patient breathes chamber air. Treatments are daily, Monday through Friday for a planned total of 30 sessions. Time to change in subjective study outcomes (relief of joint pain, stiffness, improvement in sleep patterns, and increase in activity level) will be documented. Treatments will stop at the end of 30 sessions whether or not there is subjective improvement. After the initial assessment, follow-up with the rheumatologist is scheduled at three and six months which is standard of care for rheumatology patients. If the participant

experiences subjective improvement during the 30 hyperbaric sessions, he/she will be assessed by one of the rheumatologists at the time of improvement. The hyperbaric physicians will be monitoring the patients daily, five days/week, and provide ongoing clinical assessments during the hyperbaric treatments. This is standard of care for HBO2 patients.

If the patient's RA symptoms worsen during the study, the plans are to:

1. Schedule an appointment with the the Hyperbaric and Rheumatology physicians to clinically evaluate and determine the cause. If it is determined that the symptoms could be due to HBO2, the treatment will be stopped and the Research Monitor will be notified.
2. The physicians will institute measures to address the cause.
3. If cause cannot be diagnosed and symptoms persist despite appropriate measures and if believed the patient may worsen from continued HBO2, treatments will be suspended.
4. Any adverse events will be recorded and reported to the IRB according to the AFI 40-402 and SGSE Operating Instructions and the Medical Monitor will be notified (see Section 6.7)

6.5. Risks/Benefits:

All diagnostic and therapeutic procedures associated with subject qualification for, or participation in this study will be documented in standard patient record format. Copies of documentation will be placed in both the patient's medical record and the associated patient study record.

Risks/ Inconveniences:

Middle ear barotrauma and eustachian tube dysfunction is the most common side effect of HBOT with an incidence of at least 2%. Sinus barotrauma is even less common and is associated with URI or allergic rhinitis. Symptoms range from mild discomfort equilibrating pressure in the ears to actual barotrauma. The majority of patients experiencing these symptoms experience relief after the administration of nasal decongestants or nasal steroids and can complete the hyperbaric therapy. To mitigate against this known risk, patients receive detailed instruction in the proper methods for equilibrating the pressure in the ears and sinuses prior to hyperbaric therapy.

Claustrophobia appears to be present in about 2% of the general patient population, and may be higher even in the multiplace and mono-place chamber. True claustrophobia causes people to sweat and experience tachycardia in elevators, CT scanners and MRI machines. Study participants with true claustrophobia will be excluded from the study. It is far more common for people to experience confinement anxiety, rather than true claustrophobia. The majority of patients experiencing confinement anxiety are able to complete hyperbaric therapy sessions without difficulty. Study participants who are unable to overcome the symptoms of confinement anxiety will be allowed to complete the study and occasionally, sedation will be used if the participant has people available to drive them to and from the DGMC.

Vision changes, typically a progressive myopia, can occur in some patients undergoing prolonged treatment courses of HBOT. The exact mechanism is unclear, but is apparently lenticular in origin. The incidence documented in the literature ranges from 20% to as high as 69%, with complete reversal of the refractive changes occurring in nearly all patients except those with pre-existing cataracts. Refractive changes developed in 24 of 25 patients studied in Sweden, undergoing prolonged courses of HBOT of 150-850 daily exposures. With one possible documented exception, new cataracts do not develop within clinical courses of 20-50 sessions.

Pulmonary barotraumas with or without air embolism may rarely occur during decompression, necessitating careful analysis of risk versus benefit. The actual risk is indeterminate, but is known to be higher in patients with asthma or pulmonary blebs. To protect against these risks, the DGMC hyperbaric chamber does not permit wheezing asthmatic patients to enter the hyperbaric chamber. This risk is minimal for controlled asthmatics that are compliant with their medication. Similarly, a chest x-ray and pulmonary consultation will be required of any patient with known pulmonary disease who wishes to enroll in the study. Any participants with known pulmonary disease who wish to enroll in the study will be permitted to do so if they are cleared by their pulmonologist.

Cardiovascular responses and flash pulmonary edema are rare complications of unknown risk and unknown incidence due to the rate-dependent reduction in cardiac output with an increase in peripheral vascular resistance that hyperbaric oxygen induces. These effects are well tolerated by normal individuals, but patients with decreased left ventricular ejection fraction must be monitored for the rare complication of acute pulmonary edema. In as little as ten minutes, these changes in cardiac output can lead to a collection of fluid in the lungs known as flash pulmonary edema. The incidence is unknown. The current inability to accurately identify patients susceptible to this rare complication requires careful evaluation of known heart failure patients prior to hyperbaric therapy. Potential study participants with known heart failure will be required to have an echocardiogram and a cardiology consultation prior to enrolling in the study. Study participants with heart failure will be allowed to enroll in this study if they are cleared by their cardiologist.

Oxygen associated risks include central nervous system toxicity manifest by focal and or generalized seizures. Recent surveys that include a total of 138,968 patient therapies at three different facilities indicate a combined incidence of ~ 0.03% for three 30-minute oxygen breathing periods at 2.4 to 2.5 atm abs. Earlier estimates of the seizure rate during HBO exposures at 2.0 to 3.0 atm abs reported a convulsion incidence of 0.01%. HBO2-induced seizures only occur during the exposure to high levels of O2 in the hyperbaric chamber at pressure, and there are no residual effects. However, if not diagnosed and managed, seizures can recur on re-exposure to HBO2.

Hypoglycemia: In diabetic patients taking hypoglycemic medications, there is a risk of hypoglycemia and associated effects. To protect against this complication, the DGMC hyperbaric policy requires blood sugar levels of at least 120 in diabetic patients prior to

receiving hyperbaric therapy. Diabetics with blood sugar below this level receive juice and crackers, and may have blood glucose rechecked prior to therapy. Hyperbaric staff are always present in the hyperbaric chamber, and can monitor for signs or symptoms of hypoglycemia. At least one member of the hyperbaric team is present in the chamber for each eight patients in the chamber. If symptoms occur, staff will recheck the blood glucose immediately, and administer juice and crackers if needed. Following the completion of hyperbaric therapy, diabetic patients are again tested for blood sugar level. Patients must have a blood sugar level of at least 100 prior to leaving the hyperbaric medicine department, or be cleared by the hyperbaric physician.

Fire is always a risk with pressurized oxygen in high concentrations. Hyperbaric chamber patients are not allowed to smoke or carry lighters or flammable materials in the hyperbaric chamber. Until a recent explosion in a non-certified chamber, there had not been a fire in a United States hyperbaric chamber since 1968.

There is an **inconvenience of the time** associated with the study. There are approximately 40 appointments over a six month period. Thirty of them are two hour appointments for hyperbaric treatments.

Blood draws: there is a risk associated with blood draws. The risks of taking blood include: Pain, bruise at the point where the blood is taken, redness and swelling of the vein, infection and a rare risk of fainting.

Ultrasound: There is no risk associated with ultrasound.

MRI: We will be doing a MRI with and without contrast looking at the wrist from the distal radius to the mid diaphysis of the proximal phalanges. Risks include allergy to MRI contrast which is extremely rare. There is a risk of nephrogenic systemic fibrosis with poor renal function (GFR<30) that is screened for (see Attach 11) if the subject is over 50 years of age or has a history of renal insufficiency.

Benefits:

The purpose of this study is to determine the effectiveness of HBOT on rheumatoid arthritis. The use of HBO2 in patients with RA may or may not include decreased joint pain, increased activity level, improvement in sleeping patterns. Depending on study outcomes it may benefit society, possibly diminished need for use of immunosuppressive rheumatologic medications.

Risk to Benefit Ratio:
Risks are well understood, treatable and with few exceptions of low magnitude. The potential benefits such as reduction in pain, improved sleep, decreased RA disease activity are extremely beneficial. As such, potential direct benefits to the subjects and to future treatments outweigh the risks that, as mentioned above, are rare and minor in the well-selected patient.

6.6. Subject Population

Age Range:	☒ ≥ 18 y/o	☐ Children (≤ 18)
Sex:	☒ Male	☒ Female
Vulnerable Population:	☒ No	☐ Yes (explain)

Number of Subjects:

- Total Number of Subjects: 20
- Number of Subjects Planned for DGMC: 20

A total of up to 20 subjects will be recruited. We will continue to recruit and treat until 10 complete data sets have been obtained. In the event that ten total data sets are obtained and additional subjects are in the process of the intervention, at the PI's discretion, those additional subjects will receive full treatment.

Inclusion/Exclusion Criteria:

Inclusion Criteria:

1. Age ≥ 18.
2. Active duty or DoD beneficiary
3. Diagnosed with rheumatoid arthritis meeting ACR/EULAR 2010 classification criteria and any one of the following:
    a. Patient does not want to be on rheumatologic medications.
    b. Patient has contraindications to standard rheumatologic medications.
    c. Patient has failed treatment or an incomplete response with standard rheumatologic medications.
4. Women of childbearing age must have a negative pregnancy test and currently be on a reliable form of birth control.

Exclusion Criteria:

1. Severe depression
2. Dementia, mental disability
3. Claustrophobia
4. Uncontrolled seizure disorder
5. Uncontrolled asthma/severe COPD with $pCO_2 > 45$ mmHg on arterial blood gas
6. Grade 4 congestive heart failure
7. Unstable angina
8. Chronic/acute otitis media/sinusitis
9. Major tympanic membrane trauma
10. Severe kyphoscoliosis
11. Prior chemotherapy with Bleomycin and evidence of deterioration in diffusion capacity of the lung for carbon monoxide (DLCO) after a single hyperbaric oxygen exposure.

12. History of renal insufficiency or GFR< 30
13. Women that are currently pregnant or breast feeding or intend on becoming pregnant while enrolled in the study

Recruitment:

1. Current or prior patients of the Rheumatology Clinic will be recruited by Rheumatology Clinic which is located in the Internal Medicine Clinic.
2. IRB-approved HIPAA waiver to contact patients that have been seen in the military treatment facility (MTF) within the past year with a diagnosis of rheumatoid arthritis
3. Flyers in the Rheumatology Clinic patient rooms.
4. Investigators may make an announcement at commander's calls after appropriate approvals have been made.

Consent:

Adequate study staff time will be set aside for each participant to receive information, ask questions and consider participation in the study. The consent process will begin with the introduction of the study. The Principal Investigator or study staff that have been delegated responsibility and have been trained on the protocol and consenting process, will explain the nature and scope of the study, potential risks and benefits of participation in lay terms and answer any questions the subject may have. At this point the subject will be asked to read the Informed Consent Document (ICD) and Health Insurance Portability and Accountability Act (HIPAA) authorization. If the subject has any further questions, they will be answered. When the subject has had all his/her questions answered, he/she will be offered the opportunity to participate in the study. If the participant has further questions, and wants to talk to a physician, one of the physicians on the study will be available to meet the prospective subject and answer any questions. This information will be discussed in a private area of the hospital or doctor's office.

The subject may elect to discuss the study with others if they so choose, prior to agreeing to participate. If the subject agrees to participate, the IRB approved ICD and HIPAA consent must be signed and personally dated by the subject and Investigator or study staff who have been delegated the responsibility and have been trained on the protocol before any study related procedures are done.

The original signed consent form will be turned into the protocol office and a copy will be placed in the subject's study folder and stored with other protected health information in a locked filing cabinet in an office that is locked when the office owner is not in the room. A copy of the ICD will be placed into their electronic medical record as well. Subjects will be assured that they may withdraw from the study at any time and for any reason and their medical treatment will not be compromised. Research procedures will not start until the IRB approved informed consent document has been signed and dated by the subject and research team member who has been delegated responsibility for consenting subjects and has been trained on the protocol.

6.7. Safeguards for Protecting Subjects:

The Medical Monitor as per 32 CFR 219.109 (e) and IAW DODI3216.02_AFI 40-402 will serve as the subject advocate and ombudsman. He will have the right to discusses research progress with the principal investigator and staff. He will coordinate and review adverse event reports with the principal investigator. He may interview and consult on individual cases and reports to the IRB/PI any discrepancies or problems. The Medical Monitor may stop the research study in progress, remove individual subjects from a study, or take whatever steps are necessary to protect the safety and wellbeing of research subjects. The Medical Monitor will have the right and duty to review the study progress at varying intervals.

This study involves greater than minimal risk to subjects with the possibility of adverse subject reaction to the therapy. Primary monitoring of the study will be performed by the study team members, who will review accrual, adverse events (AEs), and treatment on a real-time basis. They will ensure that all eligibility criteria and consent requirements are met prior to a subject's participation in the study and that all study procedures and adverse event reporting occur according to the IRB approved protocol. They will follow all study participants, while on study treatment, on a real-time basis for development of adverse events and study endpoints, utilizing scheduled and as needed physical examinations and laboratory studies. Potential adverse events for this study are specifically listed in section 6.5.

Any event will be graded by severity and outcome. Study staff will make certain that all adverse events are recorded and reported according to DODI3216.02_AFI 40-402 and SGSE Operating Instruction 40-402-01. Cumulative adverse events and study toxicities will be reviewed weekly. The study team will make decisions regarding treatment, cessation of accrual, and whether or not to close the study on the basis of frequency or severity of UPRISOs, Serious Adverse Events (SAEs). Any deviation, cessation in accrual or early study close will be communicated to the IRB immediately.

All SAEs, not related to progression of underlying disease, will be reported to the IRB immediately and when appropriate, the participant will be dis-enrolled from the study. All Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) related or possibly related to the study will be reported by the PI/designee to the IRB according to SGSE Operating Instruction 40-402-01.

All study staff members will be informed by direct personal communication about any UPIRSOs or SAEs. If any protocol changes are needed, the PI will submit a modification request to the IRB. Protocol changes will not be implemented prior to IRB approval unless necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB will be promptly informed of the change following implementation (within 5 working days).

Serious adverse events can occur inside the hyperbaric chamber that can be either related, or unrelated to the exposure. Whenever an adverse event occurs, a stand-by hyperbaric staff

member will immediately be compressed in one of the connected chambers, enter the main treatment chamber, and accompany the patient to the transport chamber to be decompressed to the surface for definitive medical care. If necessary, an appropriate code can be called, or the patient may be immediately transported to the emergency room for further management.

Standard measures for protection of subject privacy and confidentiality that are currently being practiced will continue. All electronic data will be housed on a Common Access Card enabled computer accessible only to study personnel within a secured office. All access to the subject computer will be logged. All electronic transmissions of data will be encrypted over a secured network. All electronic data and hard copy records obtained as a result of the HIPAA waiver, will be deleted or shredded after contact has been made or no contact has been successful. All hard copy records will be stored in a locked hyperbaric medicine file cabinet in a secure room for the duration of the study. Upon the close of the study all records will be transferred to the CIF for storage for three years then staged to storage according to IAW DODI 3216.02_AFI40-402 and USAF policies.

Incidental Findings

All study participants will receive a complete history and physical examination by a Rheumatologist at the start of the study and abbreviated history and physical examinations at each visit thereafter. Each participant will have a history and physical examination by a hyperbaric physician to determine appropriateness for hyperbaric oxygen exposures. During these assessments, patients occasionally complain of symptoms unrelated to the study purpose. During the physical examinations, it is possible that a secondary condition will be detected. When unrelated medical conditions are detected or suspected by the hyperbaric physicians, the subject will be referred to their provider and may be referred to an appropriate physician for further evaluation. A report of all incidental findings will be entered into a written report that will be placed in the subject's electronic medical record

Previously undiagnosed medical conditions that are discovered unintentionally and are unrelated to the current subject of research will, when actionable, be reported to the IRB in a timely manner based upon the suspected condition or disease severity. In coordination with the IRB, and a qualified specialist the PI will verify the finding. Depending upon the severity of the condition or disease the subject or subjects legal representative will be contacted by the PI via phone or letter or an in person communication.

Data Entry: Data will be entered by authorized study personnel only. Upon completion of data entry all hard copy documents will be stored as per the hard copy records policy outlined below. All electronic Protected Health Information (PHI) data will be housed on the DGMC EPHI drive and will only be accessible via a Common Access Card enabled computer accessible only to study personnel within a secured office. All electronic transmissions of data will be encrypted over a secured network.

Data security and transfer: Study documents will reside in the Clinical Investigation Facility within the 60MDG SGSE Directory in a limited access password protected directory designated

exclusively to the study. Access will be granted only to study personnel.

To be in compliance with Government regulations study personnel will utilize 128 bit AES encryption. AES is widely used across the government healthcare sector to secure data-at-rest, data-in-motion and data-in-transit. All data transfers will be made via (password protected CD, encrypted Electronic Mail, Secured FTP server, other). All data files will utilize the Advanced Encryption Standard approved cryptographic algorithm used to protect electronic data.

Hard Copy Records: A copy of the IRB approved informed consent signed and dated by the volunteer and designee will be provided to the study volunteer. The original signed and dated IRB approved informed consent form will be placed with other study records, in a locked cabinet and secured area within the IRB Protocol Office at the Clinical Investigation Facility. A copy of the signed ICD will be in the coordinator offices located in the Internal Medicine Clinic. These records will be accessible only to study personnel, the IRB, and employees of authorized Federal departments and regulatory agencies. Duplicates will be provided to the volunteer upon written request.

All subjects will be treated in compliance with DODI3216.02_AFI 40-402 and applicable FDA and DHHS guidelines.

All biologic specimens will be maintained at David Grant Medical Center and will be handled and disposed of in accordance with federal regulations.

6.8. Data Collection/Analysis:
This is a pilot study with 10 participants with complete data sets
Demographic information will be collected including sex, age and ethnic background in accordance with HIPPA compliance.
Data collected during this study will be analyzed at various points in time to include physician exams, labs (CRP, ESR, Basic Metabolic Panel, analysis of Microparticles, neutrophil and platelet activation, radiologic studies, joint inspection.
Changes in joint pain will be determined by self-reporting and results of the standard outcome measures questionnaires (the RAPID 3, PSQ-3 and Visual Analog Scale for pain).
A separate sleep survey will be administered.

Source of Research Material per Participant:

Source of Research Material per Participant	Standard Care	Research Driven
Blood Sample – ESR	0	5
Blood Sample CRP	0	5
Metabolic Panel	0	3
Microparticles	0	5
Ultrasound/ MRI	0	3
Questionnaires	0	9

Lab sample for analysis of Microparticles, neutrophil and platelet activation will be sent to:
name/contact information **redacted** 28 Jan 2020

7. Conflict of Interest
NONE.

8. Investigation Schedule

	Y1 Q1	Y1 Q2	Y1 Q3	Y1 Q4	Y2 Q1	Y2 Q2	Y2 Q3	Y2 Q4
Recruitment	X	X						
Enrollment	X	X	X					
Baseline Data		X	X	X				
Treatment			X	X	X	X		
Data Collection			X	X	X	X		
Statistical Analysis					X	X	X	
Publications/Reports						X	X	X

9. Use of Investigational Drug(s) ☒ No ☐ Yes

10. Use of Investigational Device(s) ☒ No ☐ Yes

11. Support Required

Pharmacy Support: Non applicable, no medications will be given.
Contact the pharmacy early in protocol development phase of your study if drugs are involved.

Drug or Placebo	Investigational?	Which pharmacy will prepare?	Support letter attached?
N/A	N/A	N/A	No

Lab Support:
Request CLIA certificates from all laboratories for your files.

Test Name	Standard Care?	Which lab will perform each test?	Support letter attached?
CRP	No	DGMC	Yes
ESR	No	DGMC	Yes
Metabolic Panel	No	DGMC	Yes
Microparticles	No	University of Maryland	N/A

Radiology Support Required:
If radioisotopes or radiation-producing equipment will be used, describe here.

Procedure	Standard Care?*	Which facility will perform proc.?	Support letter attached?
Ultrasound	No	DGMC	Yes
MRI	No	DGMC	Yes

*** Any Radiation exposure that is not standard care requires Radiation Safety Committee review.**

Nursing Support: N/A

CIF Support: Consultation, biostatistics, research coordination and administrative support.

Other Support: Hyperbaric Clinic participation for the administration of 30 HBO2 sessions with accompanying monitoring.

12. Budget, Equipment, and Supplies

Requesting Funds: ☐Yes ☐No

☐R&D ☐O&M ☒HMJ ☐OTHER (explain source):

Study Year	Item Description	Unit of Issue (UOI)	Cost/UOI	Quantity	Total Cost
2016	N/A				
2017	Labs for Microparticles		55	50	2750.00
2017	Fed Ex		28.90	50	1445.00
2018	Labs for Microparticles		55	30	1650.00
2018	Fed Ex		28.90	30	867.00

☒ I understand that the funding is the responsibility of the PI, which includes; management, tracking, recording and must be reported to the IRB annually with your continuation report

13. Manpower

Estimate the number of work hours to be applied to the investigation, categorized by Air Force specialty code (AFSC).

Rank	AFSC	# hours duty time	# hours off-duty time
names	44M	35	0
redacted 28	CTR	70	0
Jan 2020	44M	25	0
	44R	40	0
	44R1	40	0

	Consultant	30	NA
names redacted 28 Jan 2020	CTR	55	0
	CTR	5	0
	CTR	40	0
	CTR	5	0
	CTR	5	0

14. Institutional Official (IO)

(name/contact info redacted 28 Jan 2020)

15. Bibliography

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16. Attachments:

1. Informed Consent
2. HIPAA consent
3. Certificate of Compliance
4. Laboratory Support Letter
5. Hyperbaric Clinic Support Letter
6. CIF Support Letter
7. Radiology Support Letter
8. CVs and NIH/ CITI training

9. Recruitment flyers
10. Surveys (DAS28, PSQ-3, VAS scale for pain using a grid & numbers)
11. MRI Screening form
12. RAPID 3
13. HIPAA Waiver
14. Patient Letter

17. Commander's Acknowledgment of Review and Approval

Principal Investigator: I am aware that I am not authorized to accept any funds or other form of compensation for conducting research. All subjects will be treated in compliance with applicable Air Force, DoD and federal regulations, as well as applicable FDA and DHHS guidelines. I have read, understand, and signed the attached Certificate of Compliance. I understand I must complete a review of this protocol at least every 12 months to prevent expiration of the study's approval. I will notify the protocol office **prior** to relocations, separation actions, or closure.

☐ Initial Submission
(ALL signatures required)

☒ Amendment Submission
(PI signature ONLY)

(name/signature redacted 28 Jan 20) Lt Col, USAF, MC
Rheumatology Staff

2/21/2019
Date