Indiana Veteran Recovery Pilot

...a Multicenter (up to five [5] sites) Pilot of Hyperbaric Oxygen Therapy (HBOT) at Low Pressure in Chronic Traumatic Brain Injury (TBI)/Post-Concussion Syndrome (PCS) and TBI/Post-Traumatic Stress Disorder (PTSD)

Where work will be performed:

All hospitals or health care facilities (provider) in the pilot currently operate hyperbaric chambers meeting all state and federal regulations. Determination will be made after negotiation and acceptance of the conditions and specifications identified in this pilot by the hospitals or health care facilities.

Program Description:

1. The health care providers to be selected will need to have their medical facility already approved by Indiana:
    a. Which meets the Section 501 IRS code.
    b. Employs doctors and physical therapists licensed in Indiana under IC 25-27.
    c. Treats patients with long term, chronically ill, and short term care needs.
2. This pilot has proven significant and sustained improvement to individuals with brain injuries in Israel, and as used in application and trials in the United States. This pilot intends to address the use of hyperbaric oxygen therapy at 1.5 atmospheric pressure to significantly improve patients suffering the debilitating effects of traumatic brain injury, post traumatic stress “disorder”, and other post concussive brain insults.
    a. Staffing:
        i. Staffing for this pilot will include doctors, registered nurses, and individuals trained in the application of hyperbaric oxygen therapy; hyperbaric chamber technicians trained and certified in accordance with federal and state regulations, medical clinicians certified and licensed to administer drugs as needed.
        ii. Ratio of staff to projected number of persons served may vary but usually will be an office worker, technician, doctor, and nurse treating up to two patients per site at a time.
    b. Patient selection process:

Subjects will be 18-65 years old and have been diagnosed with mild or moderate (but not severe) TBI or TBI/PTSD or PTSD by either the military (any etiology) or civilian neurologists or neuropsychologists. This diagnosis will especially include war veterans who have received the ANAM test pre- and post-deployment and had a significant decrease in their neuropsychological test scores.

Gender Restrictions

There will be no gender restrictions. However, it is anticipated that the cohort will consist mostly of males, due to the nature of the injury and the preponderance of men in the military serving in combat arms units.

Racial & Ethnic Origin

The demographics of the pilot subjects will likely mirror the demographics of the military since the pilot will likely have a high proportion of military TBI subjects. The military has a high minority representation. No

attempt will be made to limit minority involvement in the pilot nor will attempt to target particular minorities for enrollment.

Subjects will be enrolled who meet pilot criteria regardless of etiology of injury, race, or other discriminatory factors, including gender. Though there has been a preponderance of injury in the combat arms units, where nearly 100% of veterans report at least one concussive injury, about 50% of the Combat Support and Combat Service Support (like transportation and water purification and military police) report having had at least one concussive blast. This is expected to create a large cohort of female patients in the larger pilot, especially including the National Guard, because of the makeup of those units. We expect the pilot to include more men than women, but there should be a sufficient number of women to gain accurate results. There has been no appreciable difference between the sexes in civilian treatment of TBI with HBOT 1.5.

Inclusion Criteria

a. Any 18-65 year-old patient with mild-moderate TBI or PTSD. (If a military injury, subject may be active duty or a veteran. Subjects with PTSD only will be enrolled because of military medicine's difficulty in distinguishing between these patients. Also, DOD medical or Veteran's Administration disability boards will give a PTSD designation before a TBI designation because the disability rating payment scale is less for PTSD than for TBI.)
b. Have demonstrated a >20% decrement (compared to pre-deployment baseline) in ANAM composite score or specific sub-score with regard to "simple reaction time" and/or "procedural reaction time".
c. Have a diagnosis of TBI, chronic TBI/PCS or TBI/PCS/PTSD or PTSD made by a military (military etiology of blast injury) or civilian neurologist (and neuropsychologist).
d. Negative pregnancy test in females.
e. Less than 90% on the Percent Back to Normal Rating Scale. (If patient is considered 100% normal before TBI, patient should be less than 90% normal for entry into the pilot).

Exclusion Criteria

a. Pulmonary disease that precludes HBOT (e.g., asthma unresponsive to medication, bullous emphysema).
b. Unstable medical conditions that are contraindicated in HBOT (e.g. severe congestive heart failure or heart failure requiring hospital emergency evaluation or admission in the previous year).
c. Severe confinement anxiety (e.g., patients who require anesthesia conscious sedation for MRI or who cannot go in elevators).
d. Pregnancy.
e. Other pre-TBI neurological diagnoses.(seizure disorders, multiple sclerosis, Parkinson's, Lyme, etc.)
f. Participation in another experimental trial with active intervention.
h. High probability of inability to complete the experimental protocol (e.g. terminal condition).
i. Past or current history of mental retardation unless diagnosed post TBI (baseline IQ ≤ 70).
j. Pre- or post-TBI history of systemic illness with impact on central nervous system. (Principal Investigator in consultation with pilot sponsor Medical Officer will make the ultimate decision).
k. Any pre-existing chronic infection not related to battlefield injuries or government service.

Vulnerable Subjects

All subjects will be legally capable of consenting. No subjects who need 3rd party consent will be enrolled in the pilot.

Military - special care and precautions: The subjects will have to voluntarily contact participating sites or respond to a recruitment outreach outside of their command.

Homeless - special care and precautions: All state and local laws will be followed as the team works with federal, state and local homeless programs.

i. Other evaluation(s) as needed:

After a patient inquiry is received the office staff, under the supervision of the PI, will do the initial qualifications assessment and then as appropriate, will schedule the patient for a medical interview and examination. After medical examination and final qualification, they will be scheduled within one week to undergo baseline testing (characterization of initial status) and will begin the therapy within two weeks of formal entry into the pilot.

The subject's baseline will be ascertained by various means. Some of these characterizations will be specific to those patients with a military etiology. For all subjects with a head injury, the subject will be asked to characterize the nature of the injury (time, date, place, circumstances, loss of consciousness, residual symptoms). For those with a blast injury, we will ascertain, for each exposure, the approximate time, place, distance from the blast, body orientation with regard to the blast, and frequency of exposure. We will determine if there was any loss of consciousness, medical characterization of same, time course of recovery, and residual symptoms.

In addition to above, for military etiology TBI, the patient's diagnosis according to the military physicians will be ascertained, along with any revision during treatment. Specific forms will be used to characterize the military exposure (see below).

Screening
To determine qualification for the pilot, patients will be questioned by the site investigator (or staff under direct supervision of the PI) using simple screening questions to determine qualification for the pilot, regarding hyperbaric oxygen therapy, absolute and relative contraindications, and other inclusion and exclusion criteria. Upon their initial medical evaluation, they will then be consented by the site PI and complete the Michigan Alcohol and Drug Screening Tests (DAST) to characterize any level of substance abuse, the PTSD checklist to identify and verify the presence or absence of PTSD in TBI subjects, the automated tests ANAM and CNS-VS. All patients to receive blood analysis before and after treatment of HBOT.

All subjects will proceed to evaluation with the tests to be described below. Subjects will be urine drug tested prior to enrollment and tested for pregnancy (monthly) then will complete QOL questionnaires that are described below. They will undergo neurological exam and hyperbaric medicine exam by the PI. They will be asked if they have had recent pre-post deployment ANAMs, imaging or full neuropsychiatric testing - if so, these data will be collected from subject.

Disability Rating Scale
The Disability Rating Scale is a well-characterized instrument that reliably reflects general outcome in moderate to severe TBI and has been shown to correlate with electrophysiological measures of brain injury.

Hyperbaric Medical Exam
This exam will be performed by the site PI. It will be another layer of screening of the subject for overall fit to the pilot as well as assessment of hyperbaric medicine exclusions. Patients will also be instructed in how to clear their ears during chamber pressurization.

Neurological Exam
The neurological exam will be performed by the PI. The patients will be questioned for previous neurological disease. Neurological exam will emphasize balance and gait, two functions that have been found to be abnormal on physical exam in patients with mild or moderate chronic TBI.

Then, subjects will begin to undergo HBOT sessions at 1.5 atmospheres absolute (ATA) for 60 minutes once daily, 5d/week. For persons who have to travel, a modified protocol of twice daily for the first two weeks and once per day thereafter six days per week may be followed to shorten the travel expenses.

Subjects will undergo automated testing (ANAM, and CNSVS) neuropsychiatric testing and complete forms needed for monitoring purposes upon enrollment. Testing will be repeated after 20 and 40 hyperbaric treatments. If necessary, some tests may need to be repeated (i.e., ANAM) to stabilize the results from the learning effect.

At the conclusion of 40 HBOT's the subjects will complete the PBNRS. If the score is ≥ 90% the subjects will have a repeat automated psychometric test battery, QOL questionnaires, urine drug testing, and pregnancy testing.

If the PBNRS is < 90% the subjects will have another 20 HBOT's on a 5-6 HBOT/week schedule and repeat the automated tests.

Six months after final HBOT subjects will be questioned by the PI (or by staff under supervision of PI) preferably in-person, or by phone or internet, regarding return to work or school and PBNRS. They will repeat the automated tests at this point.

Long-term follow up beyond this period will be enabled by phone and online automated testing; the patients will be requested to complete the automated tests for up to 2 years.

Alcohol and Drug Abuse Assessment at Baseline and During Treatment / Michigan Alcohol and Drug Screening Tests
MAST & DAST are standardized measure of lifetime and current substance or alcohol abuse or dependence. Patients with severe scores will NOT be excluded from this pilot if they have past or current histories of significant substance/alcohol dependence or abuse. Higher severity scores are associated with more severe addictive symptoms on this measure, which could confound evaluation of any HBOT treatment effect. They will be tracked as such.

Psychometric Testing
To facilitate the scale of this pilot and to allow more frequent evaluation, it is necessary to rely primarily upon automated computerized internet-based neuropsychological tests and questionnaires.

Neuropsychological tests and Quality of Life Questionnaires will be administered to each participant. The screening measures will be used to characterize the patients using diagnostic measures used by both the military and civilian diagnosticians.

The neuropsychological tests in this pilot are utilized for three purposes: 1) as pre-tests to measure each participant's baseline level of neuropsychological functioning including: intellectual functioning, memory, executive abilities, psychomotor speed and coordination, and psychosocial/adaptive functioning prior to HBOT, 2) as post-tests to measure the effects of HBOT on the neuropsychological measures listed above, and 3) to measure constructs which serve as moderators for the effects of HBOT, including IQ, personality, and adaptive functioning.

Since TBI consists of both focal and diffuse injuries, different patterns of cognitive, neurobehavioral, and adaptive functional impairments are found that contribute to heterogeneous courses and outcomes. In our experience HBOT has differential effects on these impairments that vary individually. To capture the heterogeneity of both the TBI and HBOT response, we will use multiple pre- and post-treatment neuro-behavioral and adaptive functional measures.

Imaging
No imaging is done or required as part of this pilot. We will be careful not to interfere with the patient's medical care except to provide HBOT and automated neuropsychometric testing as part of this pilot.

If the patient has imaging (recommended by their physician outside of the pilot) after enrollment, we will make every effort to have the patient undergo the standard set of automated neuropsychological tests (ANAM and CNSVS) again within one week of any imaging studies.

Characterization of Subject's Military Experience and Etiology of Injury

PTSD Checklist PCL-M
The PCL is a 17-item self-report measure of the 17 DSM-IV symptoms of PTSD. Respondents rate how much they were "bothered by that problem in the past month". Items are rated on a 5-point scale ranging from 1 ("not at all") to 5 ("extremely"). PCL is the PCL-M (military). The PCL-M asks about problems in response to "stressful military experiences."

3Q DVBIC
The purpose of this screen is to identify service members who may need further evaluation for mild traumatic brain injury (MTBI). Screen should be used with service members who were injured during combat operations, training missions or other activities. The 3 Question DVBIC TBI Screening Tool, also called The Brief Traumatic Brain Injury Screen (BTBIS), was validated in a small, initial pilot conducted with active duty service members who served in Iraq/Afghanistan between January 2004 and January 2005.[1]

Combat Exposure Scale (CES)
The Combat Exposure Scale (CES) is a 7-item self-report measure that assesses wartime stressors experienced by combatants. Items are rated on a 5-point frequency, 5-point duration, 4-point frequency or 4-point degree of loss scale. Respondents are asked to respond based on their exposure to various combat situations, such as firing rounds at the enemy and being on dangerous duty. The total CES score is calculated by using a sum of weighted scores, which can be classified into 1 of 5 categories of combat exposure ranging from "light" to "heavy." The CES was developed for easy administration and scoring; it is useful in both research and clinical settings.[2]

Documentation of TBI Cognitive Deficits

Rivermead Post Concussion Symptoms Questionnaire
The Rivermead Post Concussion Symptoms Questionnaire[23] measures the severity of PCS in TBI. It has been shown to reliably identify those patients with chronic cognitive deficits.

Automated Neuropsychological Testing

ANAM
ANAM is a proven computer-based tool designed to detect speed and accuracy of attention, memory, and thinking ability. It records a Service Member's performance through responses provided on a computer.

[1] (Schwab, K. A., Baker, G., Ivins, B., Sluss-Tiller, M., Lux, W., & Warden, D. (2006). The Brief Traumatic Brain Injury Screen (BTBIS): Investigating the validity of a self-report instrument for detecting traumatic brain injury (TBI) in troops returning from deployment in Afghanistan and Iraq. *Neurology, 66*(5)(Supp. 2), A235.
[2] (Keane, T., Fairbank, J., Caddell, J., Zimering, R., Taylor, K., & Mora, C., 1989)

***CNS Vital Signs*:**
Verbal Memory (VBM) and Visual Memory (VIM) Tests: Vital Signs includes parallel tests of verbal memory (word list learning) and visual memory (figure learning). The tests are virtually identical, but one uses words as stimuli, the other, geometric shapes.

Finger Tapping Test (FTT): The FTT is one of the most commonly used tests in neuropsychology, because of its simplicity and reliability, and because it generates relevant data about fine motor control, which is based on motor speed as well as kinesthetic and visual-motor ability (Mitrushina et al., 1999).

Symbol Digit Coding (SDC): The Symbol Digit Modalities Test (SDMT) (Smith & Jones, 1982) is a variant of the Wechsler DSST, but the position of symbols and digits is reversed.

Neither the SDMT nor the DSST are suitable for repeated administration, because subjects are able to remember the code and thus accelerate their performance (Hindmarch, 1980).

The Stroop Test: The modification adopted for CNS Vital Signs uses only four colors/color words (red, green, yellow, blue), and only one key is in play, the space bar.

The Shifting Attention Test (SAT): The Shifting Attention Test (SAT) measures the subject's ability to shift from one instruction set to another quickly and accurately.

The Continuous Performance Test (CPT): The CPT is a measure of vigilance or sustained attention or attention over time (Rosvold & Delgado, 1956). It has been a popular test because of its robust relationship to psychiatric disorders.

Neurobehavioral & Quality of Life (QOL) Questionnaires

PRIME-MD Patient Health Questionnaire (PHQ)

Citation: The PHQ scales, including GAD-7, are free to use in clinical practice, research and education. The PHQ (and PHQ-9) are adapted from PRIME MD TODAY, developed by Drs. Robert L. Spitzer, Kurt Kroenke, and Janet B.W. Williams.

Purpose: The Patient Health Questionnaire (PHQ) is designed to facilitate the recognition and diagnosis of the most common mental disorders in primary care patients. For patients with a depressive disorder, a PHQ Depression Severity Index score can be calculated and repeated over time to monitor change.

Rivermead Post-Concussion Symptoms Questionnaire (see above)

Modified Perceived Quality of Life Scale
MPQOL is a measure of the degree of personal satisfaction with one's level of functioning across several activities of daily living.

'Percent-Back-to-Normal' rating scale (PBNRS)
PBNRS is a global measure of patient self-reported recovery or the degree to which the patient perceives she or he falls between no post-TBI or PTSD recovery (i.e., 0% = not at all back to normal) and complete post-TBI or PTSD recovery (i.e., 100% = complete recovery or back to normal).

'Return to school or work'
This will be assessed by simple questioning.

Neurological Examination

The neurological exam will be performed by the P.I. The patients will be questioned for previous neurological disease. Neurological exam will emphasize balance and gait, two functions that have been found to be abnormal on physical exam in patients with mild or moderate chronic TBI.

Imaging
Imaging is not required for participation; it is optional and may be obtained anywhere. Imaging data obtained elsewhere will be collected and reviewed upon enrollment. However, if imaging is received from patients, the results will stored in the database for potential future pilot.

c. A person-centered program:
    i. One can see from the individual testing and screening above this clinical trial is person centric.
    ii. Patient, family, and others as appropriate will be informed of actions, their purpose, and results throughout their trial.
    iii. Every individual participating will be told how they did against the goals established for them.
d. A process for initial and ongoing evaluations:
    i. Standardized measurement—see b. above.
    ii. Criteria for terminating therapy—see inclusion/exclusion criteria above. Patient can terminate at any time but they will be encouraged to continue through complete trail unless they fail due to exclusion criteria.
    iii. Satisfaction—participants will provide feedback and be evaluated as identified above.
e. Access to needed medical services and adjunctive therapy services— All procedures and therapy will be done at a hospital certified by the state of Indiana and any medical or adjunctive therapy services required are available.
f. Adequate space, equipment and facilities. All work done in connection with this clinical trial we are conducted at existing hospital(s) that provide adequate space, equipment and facilities. Thousands of Indiana residents receive hyperbaric oxygen therapy today for FDA approved medical conditions in these facilities.

HYPERBARIC OXYGEN THERAPY (HBOT) PROCESS

Subjects will be treated in various types and sizes of hyperbaric chambers. Patients may undergo treatment in either a multiplace or monoplace chamber. The above description is for the 100% monoplace oxygen chamber which will be the most common chamber used in this pilot since it is the most common chamber in freestanding and hospital-based centers.

Patients will be instructed before treatment on how to equalize the pressure in their middle ears. Once inside the chamber, just after closure of the chamber door and immediately before pressurization, the subject will be instructed to perform the first Valsalva maneuver to pressurize the middle ear space before the initial 1.5 pounds per square inch (psi) start-up pressurization of the chamber that attains air-tight “seal” of the chamber. This maneuver expands the middle ear space and brings the ear space to neutral volume after the compression effect of the initial 1.5 psi seal pressurization.

Pressurization will proceed with 100% oxygen at 1.0 pounds per square inch (psi) per minute, the lowest pressurization rate, to 1.5 ATA (atmospheres absolute) or 7.35 psi and will take approximately 7 minutes. During the entire pressurization the subject will be continuously instructed to “clear his/her ears” using various pressure equalization techniques that they have learned and practiced before chamber entry. Inability to pressure-equalize the middle ear space will immediately truncate pressurization until the subject can equalize pressure. Pressurization will then resume until the final depth of 1.5 ATA is achieved. The subject will be

notified when he/she is at treatment depth. The subject will remain at depth for approximately 45 minutes and the subject will be informed of the onset of depressurization which will occur at the same rate as pressurization. The subject will again be instructed to pressure equalize the middle ear space, however, barotrauma is minimized during decompression since gas expansion in the middle ear space passively vents through the Eustachian Tube to the pharynx. Total hatch-to-hatch dive time will be 60 minutes. The subject will be queried regarding pain and untoward symptoms after this and all subsequent treatments.

DATA ANALYSIS AND MONITORING

Administrative Coordination of All Sites

We anticipate multiple sites may participate. A main Administrative Project Coordinator (APC) will ensure consistency and accuracy among all sites [each site will have its own pilot coordinator]. All providers should be prepared and willing to play this role. Duties include:

- Oversight and Monitoring: the APC will ensure that all required monitoring of the research is scheduled, completed, and documented at the required time schedules.
- Reporting: the APC will coordinate training and insure data collection constancy.

Site Monitor

The site monitor (each site to have at least one) will perform site/clinical monitoring to assure high quality trial conduct. As such, they will perform:

- On-site monitoring of individual case histories; assess adherence to the protocol; i.e., ensuring that all subjects have gone through the appropriate consenting process and have signed the most current consent documents.
- Ensure the ongoing implementation of appropriate data entry and quality control procedures;
- Conduct a general assessment of GCPs.
- Report status to APC as required.

Data Collection, Storage & Confidentiality

Data collection and management of the master database will be performed using the CareVector Platform™ (CVP). The CVP is accessible via the Web from a site computer. Research data collected by each site will be stored locally on a site hard drive as primary data. Only persons authorized by the site PI will have access to the data on-site, and each site PI will be fully briefed on the rules of confidentiality. Concurrently, data from all sites will also be stored on the CVP, with all patient names encrypted. The only subject identifiers what will be available on-site will be encrypted file names, and these only for audit and analytical purposes.

The platform also allows for the oversight of the process and sites. It has a built in Auditor role that will support data and safety monitoring functions. Security procedures are a built-in aspect of the CVP, with multi-role and multi-site access-controls. Password protection and access privileges are granted by security administrators, each of whom has Department of Defense security clearances and who have built similar systems for DOD and the commercial sectors.

A CareVector server will house the composite database, with a backup copy stored at a remote location. All data are secured, stored and backed up according to state-of-the-art security protocols at both locations.

The platform with the database ensure that all data entered will be available for daily viewing by the co-PIs for analysis, audits, quality control, and for pilot throughout the trial. Security is provided via 128-bit SSL

encryption across all public channels; database encryption of sensitive items such as patient names and passwords; multiple border and edge firewalls; and F5 load balancing, providing redundancy and 99.9% uptime guarantee. Training and support for the CVP are provided as a part of the orientation process for the pilot and are a prerequisite for site participation.

RISK – BENEFIT ASSESSMENT

This is a no significant risk using an existing FDA-cleared HBOT device.
At a recent DOD-DCOE consensus conference on HBOT in TBI, it was the group's consensus that HBOT at 1.5 ATA 100% O2 was completely safe.[3]

General safety considerations and protection against risks
Significant adverse events will be defined as those requiring emergency department evaluation or hospitalization. Pulmonary barotrauma manifest by pneumothorax or air embolism, inner ear barotraumas with round or oval window rupture, and oxygen toxicity manifest by grand mal seizure would be the most serious adverse events, but are unanticipated. An oxygen toxicity seizure is a rare occurrence at high pressures. The low pressure featured in this pilot has not been reported to cause seizures and has been used to treat childhood seizures in China and in the United States

The most likely anticipated adverse events would be middle ear and sinus barotraumas. They are most common in the young and elderly, neither of which will be subjects in this pilot. Transient emotional liability is expected in less than 10% of the pilot group, but is managed with informed consent and bedside counseling.

Secondary gain for malingering and disability
This may be a problem in mild-moderate TBI research, the degree of malingering is difficult to assess. To prevent elimination of bona fide brain injured patients we will include all patients regardless of level of effort/malingering. Some patients may have already been given disability. It is our objective to only determine whether we can improve patients who have been given military or civilian diagnoses of chronic TBI/PCS and/or TBI/PCS/PTSD and which patients with these diagnoses will be susceptible to possible beneficial effects of HBOT. The inclusion of all can provide valuable information on the effectiveness or ineffectiveness of HBOT and identify/characterize those non-responders.

Concern About post-hoc revision of Military Disability Rating
For those who have already been disability rated by the military the subjects will be informed that their test results are private and cannot be accessed to personally identify them and re-rate their disability.

Training effect may improve performance on automated tests
We will employ measures that minimize learning effect. ANAM and CNSVS are designed to compensate for the learning effect using internal methods, such as the presentation of alternate examples. Further, we will have the subject take the test set twice before starting HBOT treatment.

Excessive amount of testing
The multiple tests are necessary due to the heterogeneity of TBI. Since there is no all-inclusive QOL measure, multiple questionnaires are necessary. To undergo the computerized test batteries the total test time is about two hours. This is substantially less than the amount of time for a full psychometric test battery.

Confinement Anxiety

[3] DOD "HBOT for TBI" Consensus Conference White Paper, 28 October 2008.

Severely claustrophobic patients will be screened out by the physician before the Rivermead questionnaire is administered. Some of these patients may do fine with larger chambers as available. Xanax, as needed, will help those who still have problems, however, this will be discontinued one week before repeat testing.

Automated Cognitive Testing
Automated cognitive testing has limitations. However, when used to monitor change over time, it is valid.

Lack of sham control group
This is an observational pilot of an off-label use of an FDA-cleared device. This is acceptable because preliminary pilot data results showing efficacy suggest that a sham treatment arm may be unethical, especially since the data demonstrate that the treatment is extremely safe. And, because the first study by Dr. Harch was a pilot, it will be followed by a second single crossover study that is about to begin in parallel with the present pilot. Longitudinal measures can be analyzed for comparison to baseline. Also, performance of the subjects in this pilot can be compared to historical data accumulated by the military on the degree of spontaneous improvement over time in their untreated injured population of servicemen and women.

Alternative Methods & Approaches
While there are other therapies that are attempted for TBI and TBI/PTSD, we know of no safe, effective alternative treatment method for traumatic brain injury.

Alternative outcome measures are numerous and formal comprehensive neuropsychiatric testing may be superior to the automated approaches proposed herein. However, due to logistical, funding, and time constraints it is not possible to obtain the most comprehensive neuropsychological analyses or all possible imaging studies and biomarkers. Rather, we will make every effort to collect information on any testing or imaging ordered by the person's physicians in the routine course of their clinical care.

HBOT 1.5 Safety versus Drugs Prescribed Off-Label for PCS & PTSD
When comparing HBOT to the common drugs being prescribed off-label for PTSD and TBI patients, the difference is remarkable. (Only Zoloft is on-label for PTSD. No drugs are approved for PCS or TBI). Many of the anti-depressants have a warning label from the FDA. The actual FDA warning reads, "Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of (insert name of antidepressant) or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24…" The age group described by this warning would seem to include a significant number of our brain-injured veterans. Thus, by getting this pilot done quickly, the investigators have a good chance of helping reduce the epidemic of suicides in the current population of casualties from the current war.

Potential benefits to the subjects
The subjects will not be given false assurance that they are likely to benefit from the procedure.

Patients will not be compensated and the pilot will be patient- or site-funded
The subjects will not be compensated for treatment. Actually, until higher levels of funding become available for this pilot, the subjects and or the site investigators will have to find private funding for their treatment as outlined in the present pilot.

Alternatives to participation
Congress has funded $1.9 billion in TBI & PTSD research since 2005. Therefore, the patient may choose to continue to participate in any one of the existing programs for patients with TBI and TBI with PTSD, using

drugs and/or complementary therapies. It should be noted that there is no drug or device currently approved by the FDA to treat TBI or TBI with PTSD.

SUBJECT IDENTIFICATION, RECRUITMENT, AND CONSENT / ASSENT

Method of Identification and Recruitment
Subjects will be recruited through multiple avenues, particularly through military/ veterans service organizations or media reports. It is anticipated that a majority of the subjects will be former military suffering from TBI and PTSD. It is anticipated provider will use media presentations to recruit subjects for this project.

In addition, PI and the participating hospitals have extensive relationships with professional societies which will be conduits to the target population. Print, radio advertisements/ announcements, and website announcements (the International Brain Research Foundation, the International Hyperbaric Medical Association, the American College for the Advancement of Medicine, the American Association of Health Freedom, the American Association of Physicians and Surgeons and others) can also be used to recruit subjects. Additionally, TBI associations and support groups will be targeted for presentations and announcements. Veterans Treatment Courts and law enforcement agencies and organizations will be contacted and encouraged to communicate the opportunity to participate.

Process of consent
Each subject will be provided the consent form and will be provided at least 24 hours to review, consider, ask questions, and sign the consent form. The subject will be provided a copy of any document they sign and two copies will be made for storage on site and at the central office of the sponsor.

Subject capacity
All subjects will have the capacity to consent to treatment. The rare subject will not be able to read due to an eye injury or brain injury. These subjects will have the consent form read to them twice in the presence of a witness and then, the reader and witness will sign the patient's consent form in lieu of the patient.

Subject/representative comprehension
Referring organizations or volunteer veterans' service organizations can receive a briefing on the pilot, risks, benefits, etc. Selected providers are encouraged to do so.

Debriefing procedures
All subjects will be briefed by the investigator or designated personnel in accordance with best medical practices for full disclosure of patient outcomes, anticipated future status, and how to return for more treatment, if desired.

Costs to the subject
The subject is responsible for 10% of treatment costs. They will not be paid for their participation or reimbursed for your time and travel.

Providers are encouraged to seek additional funding from outside sources. At this time, the State of Indiana will fund 90% of the treatment up to the grant awarded in this request. It is anticipated that grants will be approximately $95,000 per site (up to 5 sites to be selected).

Each provider will pay for all of the automated neuropsychiatric testing, coordination of the pilot, and collection of data. It is anticipated that the insurance company will not cover the costs of the treatments in this protocol, because the protocol is considered experimental.

Medicare, in particular, makes it very clear that they do not cover costs that are incurred as part of a research

protocol. This protocol is an observational protocol and the use of HBOT therapy for this condition is considered investigational – this is why the present pilot is being done.

Ancillary diagnostic testing that is NOT required by the pilot may be recommended by the subject's physician/s. For purposes of planning and estimation, the subject will be informed of the costs of testing that are NOT required in this pilot are: psychometric screening, evaluation, and quality of life questionnaires ($1000/exam; subjects who undergo testing by a neuropsychologist will have 2 or 3 of these), MRI of the brain with radiologist's reading ($2,000), SPECT brain imaging with radiologist's reading ($1,750 per SPECT; subjects will have 3 or 4 of these), and functional brain MRI (approximately $2,000 per pilot; there could be 2-3 of these tests).

The principal investigator will arrange for medical care for any emergency medical problem that the subject may experience as a direct result of their participation in this research. This will be provided on a fee-for-service basis. There are no funds available to pay for any disability, pilot related, or unforeseen complications that result from participation in this pilot or for damages such as lost wages, etc.

The costs of testing and treatment that are required for this pilot are to be outlined in the budget. There are some tests that may be recommended by the patient's physician, however, these are not part of the pilot unless expressly stated elsewhere in this consent form. Costs of additional testing, such as EEG, angiograms, MRI, CT, or PET imaging, or Doppler studies should be discussed by the patient with the ordering physician. These tests can vary in cost and may or may not be covered by insurance. These tests are not required for the pilot.

Payment for participation

The patient may significantly improve their life from the acute relief of PCS symptoms and restoration of neural function, however there is no express or explicit warranty of such. The families and individuals, however, are generally financially incapacitated by their disability and therefore third party payment may be needed. Providers are encouraged to work with community organizations, foundations, and other entities to assist patients as needed. There is no payment for participation in this pilot.