



CONTRACT: W81WH-08-D-0026, Task Order Number: 12178

**Capgemini/PwC Deliverable 13d: After Action Report for HBOT in TBI Consensus Conference**

16 December 2008

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Our services were performed in accordance with Standards for Consulting Services established by the American Institute of Certified Public Accountants ("AICPA"). Accordingly, we are providing no opinion, attestation or other form of assurance with respect to our work and we did not verify or audit any information provided to us.

Our work was limited to the specific procedures and analysis described herein and was based only on the information made available through 24 Nov 08. Accordingly, changes in circumstances after this date could affect the findings outlined in this report.

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### 1.0 EXECUTIVE SUMMARY

On 5 to 6 December 2008, the Defense Centers of Excellence (DCoE) hosted the Hyperbaric Oxygen Therapy (HBOT) in Traumatic Brain Injury (TBI) Consensus Conference at the Holiday Inn in Alexandria, VA: The purpose of the conference was to bring experts from the field of TBI, HBOT, neuro-sciences, and other health care professions together to apply current biomedical knowledge and a broad range of scientific and clinical perspectives to formulate research objectives and design to determine the role of Hyperbaric Oxygen Therapy in Traumatic Brain Injury.

Approximately 60 attendees, including neuro-physicians, hyperbarists, clinical research specialists, mental health providers, academics, and key DCoE staff attended the 2 day conference. The objectives of the conference were to:

- Gather experts in TBI and HBOT for a focused HBOT in TBI consensus conference for the first time to discuss the efficacy of this treatment in a wide range of TBI cases
- Provide an overview of Hyperbaric Oxygen Therapy in TBI
- Share Best Practices and lessons learned
- Introduce the need to conduct a randomized clinical trial to study the efficacy of HBOT
- Develop a consensus among the experts in TBI and HBOT on the methods of conducting and evaluating the RCT in HBOT in TBI

Brigadier General (BG) Loree K. Sutton set the stage for the Conference on Day 1 by providing opening remarks and welcomed special guest General James F. Amos. Presentations on day 1 included *Neurophysiology and Neuropathology of TBI; the Biological Basis and Mechanisms of Action for HBOT in TBI; HBOT in mTBI at Louisiana State University; HBOT in Acute, Severe TBI; Pilot HBOT Trial in TBI; Randomized, Controlled Trial of HBOT in mTBI; Neuroimaging in HBOT in TBI and PATIENTSD; Neuropsychological and Neurocognitive Testing in TBI: What's Measurable?; and Measurable Functional Outcomes*. Following the presentations, subject matter experts were divided into four working groups where they focused their discussions on:

- Patient Selection and End Point Analysis
- Experimental Design
- Hyperbaric Treatment Protocol
- Outcome Measures

General James F. Amos made a special appearance and gave an emotional personal account of witnessing soldiers wounded in battle who are now suffering from Traumatic Brain Injury. General Amos stressed urgency in understanding HBOT in TBI and finding relief to our wounded warriors. He understands that HBOT is a piece of the solution and wants the HBOT and TBI community to find the efficacy of this treatment. General Amos concluded his speech by introducing the keynote speaker, the Honorable Donald C. Winter, Secretary of the Navy.

Colonel Christopher Williams began Day 2 by providing administrative remarks. Following the introductory plenary session, facilitator leads from each working group provided a summary of their discussion from Day 1. After the summaries, participants returned to their working groups. The afternoon on Day 2 consisted of presentations on the working group findings and further discussion. BG Loree K. Sutton provided the closing remarks.

The full agenda is listed in *Appendix (A)*.

Experience Survey Responses are listed in *Appendix (B)*.

Conference Evaluation Summary is listed in *Appendix (C)*.

Raw notes from the four breakout sessions are listed in *Appendix (D)*.

## 2.0 KEY TAKEAWAYS AND LESSONS LEARNED

### GENERAL TAKEAWAYS

- The conference was extremely well received. Many attendees noted that they learned something new from this conference. Others commented that there is little knowledge in this field and that a study of this kind was long overdue. It is evident that there is still much to be done in the area of HBOT in TBI, specifically in the area of treating mild TBI with HBOT.
- Most participants were impressed with the way the breakouts were conducted. Some had specific kudos for the facilitators' role in helping to achieve consensus on tough and possibly contentious topics.
- Participants mentioned that the conference was "well organized" and "impressed with the diversity of expertise to focus on a tough topic."
- Attendees appreciated the wrap up at the end of the first and last day to help them understand the study objectives of other groups which allowed them to gain a sense of positive achievement.
- Many key objectives were detailed and agreed by a consensus of the experts.

### LESSONS LEARNED

- Allow the working group facilitators from each breakout group to meet and communicate notes to reduce redundancies in topics discussed in the wrap up sessions.
- Establishing "Ground Rules" at the start of the breakouts worked well, especially when the facilitator asked for additional input from the participants.
- Stating the objectives and writing them on a flip chart at the start of the breakout sessions set the tone of the session.
- Reduce the possibility of "groupthink" by using anonymous voting techniques instead of counting votes by "show of hands" technique.
- Prepare PowerPoint slides of the presentations and include them in the Conference Guidebook.
- Request unqualified attendees to be excluded from the breakout sessions.
- Communicate conference objectives clearly at the beginning of the conference with measurable metrics and timelines.
- Make sure that the breakout groups have the necessary experts to facilitate discussions.
- Discuss Way Forward recommendations with participants before conference adjourns to set future expectations and action items.

### 3.0 NEXT STEPS

The following is a list of next steps following the conference:

Items	Responsible Party
Schedule After Action Report (AAR) Review with COL Williams to determine how information provided can inform the DCoE, HBOT Steering Committee, specifically with regard to planning for the next step in planning for the randomized controlled trials.	DCoE TBI and Capgemini/PwC
Develop IPR schedule for 2nd HBOT Consensus Conference to include review and discussion of Logistics AAR.	DCoE TBI and Experient
Send Thank you note to all speakers and presenters with conference feedback.	DCoE TBI Directorate
Schedule VTC to discuss Action Plan for the material decisions that were determined by the work groups and any other Parking Lot items.	DCoE TBI and Capgemini/PwC
Draft Action Plan for each of the working group subject areas; determine roles and responsibilities.	DCoE TBI
Conduct a VTC or Webcast to present the Action Plan to the HBOT in TBI study community.	DCoE TBI and Capgemini/PwC

## 4.0 SESSION SUMMARIES: DAY 1

### ***Keynote Address: 0800 - 0830***

Dr. Donald Winter provided opening remarks thanking everyone for their time and asking the focus of the conference to be on finding the best and most prudent path in treating TBI. Through the conference, he encouraged attendees to establish the best scientific treatments, identify the best candidates for safe treatment, and find the earliest possible treatment to afford the earliest possible support and to adopt the best practices to support those who have been wounded.

### ***Neurophysiology and Neuropathology of TBI: 0830 - 0900***

Dr. John Povlishock provided an overview of recovery from mTBI in humans and animals. He discussed the multiple interacting factors that determine the clinical consequences especially in early recovery from mTBI. Research on mTBI has gone to in vitro in rats and recently launching clinical trials in humans. Recent studies in pigs have shown results remarkably similar to humans. His research showed that the progression of events in rats with mTBI is more progressive than cats and more rapid than pigs.

### ***Biological Basis and Mechanism of Action for HBOT in TBI: 0900 - 0930***

CAPT Brett Hart discussed the mechanism of action in humans for HBOT. CAPT Hart discussed mechanisms to evaluate acute versus TBI. Through his work he realized that exposure to oxygen increases saturation of tissues and 90% of tissues exposed to oxygen are saturated with oxygen. In addition, blood rapidly increases with the exposure to oxygen. HBOT increases brain oxygen which can be used to mitigate hypoxic damage to the brain. CAPT Hart encouraged rapid intervention as the discovery has only been demonstrated in animals. The mitigation of hypoxic damage in humans has been demonstrated in some acute settings.

### ***HBOT in mTBI at Louisiana State University: 0945 - 1045***

Dr. Paul March discussed his work with patients experiencing mTBI at Louisiana State University. Dr. March has conducted 40 or more studies on patients with mTBI and provided 4 examples of patients treated with HBOT who all showed improvements. He concluded that HBOT has drug like effects on basic pathophysiologic processes and their diseases and that the case experience in TBI is now strongly supported by an animal model.

### ***HBOT in Acute, Severe TBI: 1045 - 1145***

Dr. Gaylan Rockswold discussed the pathophysiology of severe TBI and reviewed his previous work. Through a study he conducted, he concluded that HBOT can be delivered safely and systematically to severely injured patients, significantly improves survival, and did not improve favorable outcomes.

### ***Pilot HBOT Trial in mTBI: 1200 - 1230***

Dr. Lindell Weaver discussed a feasibility study on chronic brain injury. The goal of the study was to conduct a randomized controlled trial of HBOT on subjects with chronic stable brain injury. Results of the study showed that some outcomes appear improved, none were worse, and they could not infer that results were due to HBOT because they did not have a control group.

### ***Randomized, Controlled Trial of HBOT in mTBI: 1230 - 1300***

Dr. George Wolf discussed his journey of creating a protocol for a randomized, controlled trial of HBOT in mTBI. There were over 150 submissions of the protocol and the reviewers criticized the study for being too aggressive, but then stated the study had too few subjects and the investigators did not have sufficient publications. After comments and feedback from submission, the protocol was

modified to sham and single treatment profile (2.4 ATA). The expansion of the protocol will take place in January 2009.

### ***Neuroimaging in HBOT in TBI and PATIENTSD: 1300 - 1345***

Dr. William Orrison discussed incidents of TBI with his patients at the Nevada Imaging Center. He also showed imaging results from his 3 Tesla MRI unit. He also discussed the results of a chronic traumatic brain injury trial that looked at 100 unarmed combatants.

### ***Neuropsychological and Neurocognitive Testing in TBI: What's Measureable?: 1345 - 1415***

Dr. Michael Russell discussed measurable effects in neuropsychological and neurocognitive testing in TBI. His topics included: sensitivity, practice effects, strategies to minimize practice effects, the need for effort testing, white matter pathways, Gnostic functions, and time constraints. He also addressed how HBOT is helpful.

### ***Measureable Functional Outcomes: 1415 - 1445***

Captain Woods began his presentation on measurable functional outcomes by reviewing the definition of mild TBI. His topics included: basic cognition, post concussive syndromes, executive skills, somatic symptoms, affective complaints, behavioral changes, and functional index measures. He added some additional suggestions for outcome measures such as: return to work, quality of life, and independence.

## **5.0 MORNING SESSION WRAP UP: DAY 2**

After the plenary session, the working groups gathered in four different groups to discuss and identify key elements for a large randomized clinical trial to study the efficacy of HBOT in TBI. The working group started discussing objectives for the study towards the end of Day 1. The second day of the conference began with a summary presentation from each of the work groups on their outcomes from the previous day. The notes from the morning session Wrap Up are listed below.

### ***Outcomes Measures***

1. Restricted discussion to chronic TBI
  - a. Definition > 90 days
  - b. No limit on mTBI
2. Interested in symptomatic
3. Established Primary v. Secondary outcomes
4. 3 categories:
  - a. Biological/Neurological
  - b. Ecological
    - i. Equilibrium with patients- family discord
    - ii. Equilibrium in the community
  - c. Functional Measures
    - i. Neuropsychological metrics
    - ii. Maintain ANAM IV and impact

### ***Treatment Protocol***

1. 15 objectives
2. How many arms and levels of compression- how deep?
3. Looked at various levels of TBI- mild, acute, and chronic
4. Provide air break? How long?
5. How many treatments for each patient? How frequent?
6. If treatment is missed, how much do you allow patients to miss?

7. What about side effects?
8. Evaluated/assessed by physicians? How often?
9. Monitored throughout treatments?
10. Duration of treatment with timing- where do you start the clock?
11. 3 arms of the study:
  - a. Sham
    - i. 1.5 ATA
    - ii. 2.0 ATA
    - iii. 2.5 ATA
12. Should they initiate air breaks? How do you do that across the board?
13. Identify objectives tried to come up with treatment depths.
14. Study needs to be designed around what FDA requires.

### ***Patient Selection***

1. Reviewed chronic TBI - mild group where focusing attention
2. multi-center, blinded
3. Inclusion criteria challenge; narrowed down to combat, tour related brain injury
4. Must meet DOD category of brain injury definition
5. Less than 6 months brain injury
6. Could be 5-7 years out from war
7. Liberalizing out from where injury happened
8. Clinical interview with referral
9. Validity testing to get at notion of real injury
10. Somatic complaints at 6 months and clinician agreement that something going on
11. PATIENTSD controlled for but dealt with on front end
12. mTBI already symptomatic overlap of PATIENTSD, mTBI- symptoms are both non-specific and can't sort out
13. Mild and moderate some quandary of people- study that can help these with greatest issues or greatest numbers
14. Outcome measures will be different based on patients enrolling

### ***Experimental Design***

1. Scaffold in place- foundation depends on info from other groups
2. multi-center, multi arm controlled, blinded trial
3. Strawman in terms of questions about how arms are structured
  - a. ATM, non exposure, exposure to O2
4. Waiting for information from other groups
5. Need to know variability in terms of testing
6. Need to know sensitivity b/c statistical implications are important

## **6.0 AFTERNOON SESSION WRAP UP: DAY 2**

The working group continued their discussions on the second day of the conference and each presented a summary of their study design conclusions in a general afternoon session Wrap Up. The notes from the Wrap Up are listed below.

### ***Breakout Sessions***

#### **Outcome Measures**

1. Restricted topic to chronic mTBI, DOD definition
2. Established 3 primary outcome metrics in categories:

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- a. Domain 1: Biological/Neurological
  - b. Domain 2: Ecological
    - i. Equilibrium with patients- family discord
    - ii. Equilibrium in the community
  - c. Domain 3: Functional Measures
    - i. Neuropsychological metrics
    - ii. Maintain ANAM IV and imPACT
3. Co-morbidity psychological health and PTSD
- a. OQ-45
  - b. Structured interview scale/pai
  - c. Effort/motivational test- TOMM test

### Treatment Protocol

1. Sham arm in trial, but modified recommendation to be inclusive of trial that has arm with 1.5 and 2.0
2. To keep treatments at 60 minutes at pressure
  - a. If at multiplace chamber - start clock when end of compression and stop clock at end of decompression
  - b. If monoplace- start clock when hatch closes and stop clock when hatch opens
3. Time to compression and decompression is dependent on patients ability to compress and decompress
4. Number of treatments - total of 40 HBOT - one treatment per day at 5 days/week
5. Duration of time in which to complete protocol - all patients have up to 10 weeks to complete protocol and if don't miss any treatments, may be able to complete in 8 weeks
6. Complications for individuals -
  - a. pneumothorax - would be excluded
  - b. Oxygen toxicity seizure- would be excluded
  - c. If have claustrophobia issues, would have 10 weeks and couldn't receive drugs to help cope with phobia
7. All individuals will need chest x-ray prior to beginning treatment protocol
8. Need visual acuity just prior to start
9. All patients receive vital signs before and after HBOT
10. Create a checklist before and after HBOT - Need further discussion
11. Sham - need to resume discussions on sham protocols - Need further discussion
  - a. Minimal recompression on air in sham has proven effective with blinding in study

### Patient Selection

1. Perception that we can manipulate people in study
  - a. Reason to sign consent form- they can opt in or out
2. Have to be able to complete measurement instruments and not pay attention to whether it is mild, moderate or severe
3. Do we use psychological testing tool?
  - a. How much do they participate?
  - b. Need to complete some form of test
4. Many IRBs require true informed consent
5. Neuropsych testing only would result in a lot of missing data
6. Need inclusion criteria that they have to do 80% of outcome measures to participate
7. Patients are referred
8. Difficult to assessment functioning when they are in the barracks
9. Patients have multiple surgeries first few months- also have effects of initial surgery

10. After 6 months point- al of initial symptoms are history
11. Concern in delay of treatment is that they are getting treatment at current time- not that we are denying treatment
12. 6 months from last injury

### **Experimental Design**

1. Center - Amount of power and number of participants required to satisfy participants and amount of time to evaluate based on numbers of endpoint measurements which will tell you to increase the number of centers relative to the study
2. Prospective, randomized, double blind, stratified, parallel group, sham controlled study with a question of cross over
3. An extension would cause a problem with 6 month and 12 month follow up
4. Will take minimum of 6 months to recruit
5. Rather than interim analysis, create a data safety monitoring board that is unblended but is sequestered and periodically looking at returns of information
6. The minimal change for clinical significant movement of endpoints will show needle move
7. What degree of movement actually represents a functional change?
8. 95% confidence interval; 80% for determination of efficacy which is part of FDA requirement

**APPENDIX A: CONFERENCE AGENDA**

**DAY ONE - TUESDAY, 18 NOVEMBER**

Time	Location	Agenda Item	Speaker
0700	Hotel Lobby	Registration Opens	
0745 – 0755	Commonwealth A&B	Opening and Administrative Announcements	Colonel Christopher Williams, D.O., M.P.H., USAF Senior Executive Director, TBI
0745 – 0800		Welcome and Introduction	Brigadier General Loree K. Sutton, M.D., USA Director, DCoE
0800 – 0830		Keynote Address	Honorable Donald C. Winter, Secretary of the Navy
0830 – 0900		Neurophysiology and Neuropathology of TBI	John Povlishock, Ph.D.
0900 – 0930		Biological Basis and Mechanism of Action for HBOT in TBI	CAPT Brett Hart, M.D.
<b>Break: 0930-0945</b>			
0945 – 1045	Commonwealth A & B	HBOT in mTBI at Louisiana State University	Paul Harch, M.D.
1045 – 1145		HBOT in Acute, Severe TBI	Gaylan Rockswold, M.D., Ph.D.
<b>Working Lunch: 1145-1200</b>			
1200 – 1230	Commonwealth A & B	Pilot HBOT Trial in mTBI	Lindell Weaver, M.D.
1230 – 1300		Randomized, Controlled Trial of HBOT in mTBI	George Wolf, M.D.
1300 – 1345		Neuroimaging in HBOT in TBI and PTSD	William Orrison, M.D.
1345 – 1415		Neuropsychological and Neurocognitive Testing in TBI: What's Measureable?	LTC Michael Russell, Ph.D.
1415 – 1445		Measureable Functional Outcomes	CAPT Andy Woods, M.D.
<b>Break: 1445-1500</b>			
1500 – 1700	Wythe, Pendleton, Martin, Marshall	Working Groups	
1700 – 1730	Commonwealth A & B	Wrap Up	

**DAY TWO - WEDNESDAY, 19 NOVEMBER**

<b>Time</b>	<b>Location</b>	<b>Agenda Item</b>
0800 – 0810	Commonwealth A & B	Administrative Announcements
0800 – 0830	Commonwealth A & B	Discussion and Breakout Considerations
0830 – 1200	Wythe, Pendleton, Martin, Marshall	Working Groups
<b>Working Lunch and Sharing of Ideas: 1200-1300</b>		
1300 – 1500	Wythe, Pendleton, Martin, Marshall	Working Group Wrap Up
1500 – 1645	Commonwealth A & B	Synthesis of Study Design/Consensus Statement
1645 – 1700	Commonwealth A & B	Closing Remarks

## APPENDIX B: EXPERIENCE SURVEY RESPONSES

Participants were asked to complete an Experiences Survey to gather feedback from the participants on best practices, needs, and specific challenges. Full responses to the Survey are captured below.

### 1. What do you feel were the most valuable aspects of the conference?

- Comprehensive discussions possible over 2 day timeframe
- Collaboration and communication
- Networking, diversity of participants
- The working group that I was in was extremely professional and productive
- Healthy skepticism
- Honest discussion, however, the lobbyists, hangers on and manufacturers should not have been at the meeting
- Sharing perspectives among disparate views of the problem both with regard to definition of the issue and understanding of the risk/benefit proposition
- Deciding for a large RCT as the next step!
- The collaboration
- Working groups, closely followed by the discussion during presentations by the facilitators

### 2. What do you feel were the least valuable aspects of the conference?

- Political vs. scientific issues
- The reports back to the main group after the break out sessions were spotty in their usefulness. Some groups really didn't tell us what they had accomplished. Also, the presence of people who do not understand the scientific method in a group designed to apply the scientific method to a question was a problem.
- My discussion group had a "manufacturing rep" present. He expounded unscientific theories and was grossly unqualified to be present. He was a disruption that adversely affected the output. He almost literally had to be told not to say anything more (by the group) after what seemed to be the third time he tried to advocate his "theories." The person who allowed his presence at the meeting should be counseled.

### 3. What other comments do you have regarding the conference?

- We lacked the help of a statistician and an ethicist, both of whom could have helped us even get a little further than we did (not to criticize the tremendous progress that was made anyway)
- Would love to have the PPTs used by the presenters the first morning
- Well planned conference on short notice
- The imperative that a deliverable was necessary (i.e. the results; not the formulation of a study) should have been emphasized more emphatically. There was too much discussion about what would have been a "perfect" study and not enough emphasis on getting a working answer to the critical questions affecting our wounded warriors. It is no surprise that neuropsychologists would want neuropsychiatric testing, or that radiologists would want imaging. I did not see enough emphasis on outcome measures that directly and unambiguously addressed the quality of life issues that are important to our injured service members. I would have preferred to see more emphasis on those outcome measures (quantity and severity of headaches, quality and quantity of sleep, etc). To that end we might have been given some quantitative data as to the most

important actual complaints of those with TBI. These are the things that should be the outcome measures rather than surrogates for the degree of injury.

- Several felt that they were required to attend only for 'political reasons;' they seemed not to appreciate the urgency of the problem and the need to find a solution
- Publish the process and conference proceedings
- Wonderful job of coordinating and getting this going

#### 4. What helped to drive discussion in the breakout sessions?

- The outlines that were pre-positioned in the rooms that could be used as aids or critiqued and moved aside.
- Passion among the group to do the right thing
- The planning ahead by the facilitators to have a set of questions to be answered defined ahead of time was a great help
- Knowledgeable participants
- Unfortunately, the presence of Mr. Reimers who only expounded his theory that air embolism was the cause of injury in TBI. Here again, there was insufficient emphasis on "delivering the mail."
- Structured questions and options for response
- The agenda
- The expertise of the members invited to participate
- Expert facilitator (in my group) plus the well balanced mix of participants

#### 5. What you would recommend be changed for future conferences?

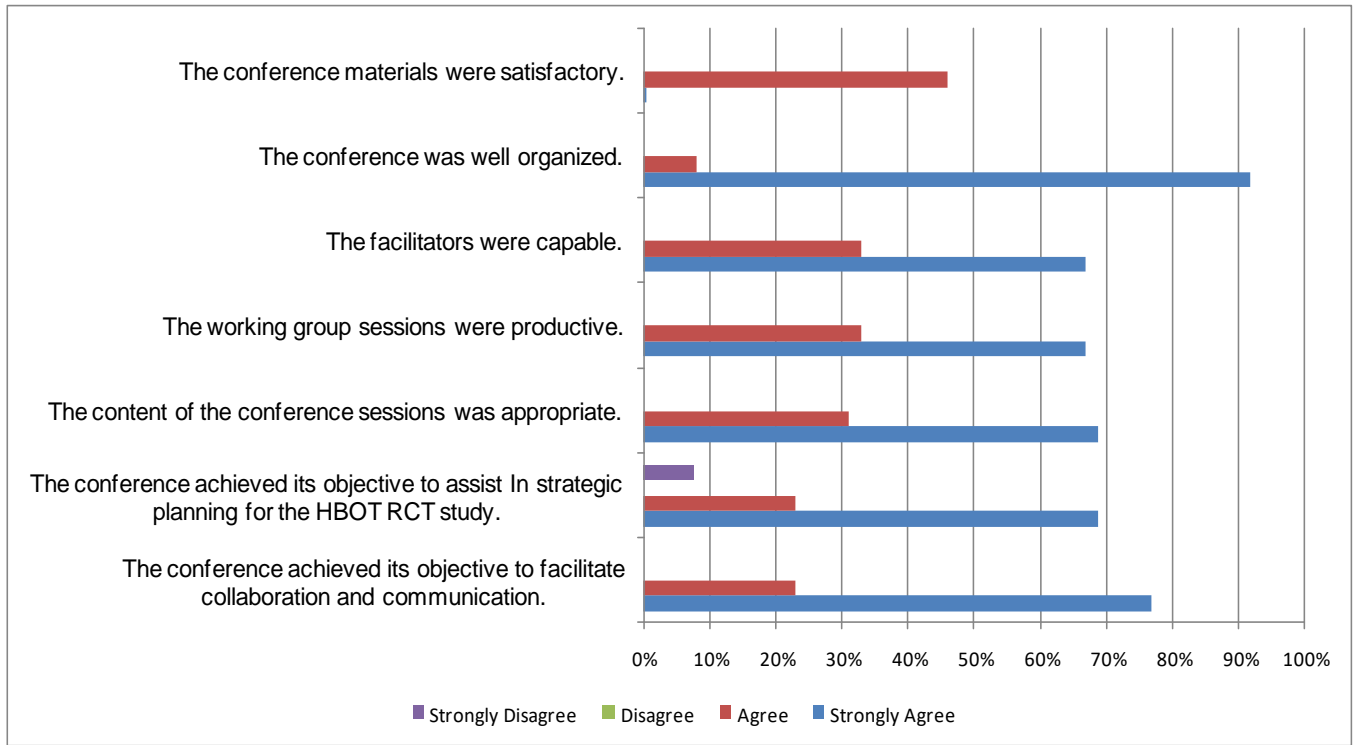
- Not applicable, this was unique
- Need to have interim periods when facilitators from each of the groups have a chance to come together among themselves to gain information on detail that is commonly needed for multiple groups to come to consensus
- Avoid having nonprofessionals (i.e. lobbyists) in the break out sessions. This was a bit disruptive as the one in question kept trying to circumvent the discussion
- A more clearly defined mission statement. Specifically including a time line for when the proposed study is completed. Clearly this is an issue on the "front burner" of the DOD. By when are results wanted? It appears the "strategic" questions have now been addressed by this conference, now specific decisions have to be made to get the project off the ground. This will require that a future conference is run by a person who is a good leader, a clinical trials expert (with first hand experience running well designed clinical trials) and a person intimately familiar with the problems of HBOT. Importantly the person who is put in charge of this must be someone with both the authority and the responsibility to make the project go forward.
- Nothing; this was a great start
- I feel non-scientific individuals should not come to such meetings
- This format did very well
- I think this was a wonderful forum and that it was handled beautifully. I cannot think of any changes that would have enhanced this conference

#### 6. Additional expertise required in break out sessions

- Ethicist, statistician
- Would have been nice to have an additional rehab expert, maybe vision or speech

**APPENDIX C: CONFERENCE EVALUATION SUMMARY**

Participants were also asked to complete an evaluation of the conference. Figure 1.0, illustrates a summary of the responses received to the Likert scale questions.



**Figure 1.0, HBOT Consensus Conference Evaluation Responses**

**APPENDIX D: BREAKOUT NOTES**

The sections below present the raw notes recorded from each of the working group breakouts. It is important to note that data captured may require further explanation. Given the variety of topics and discussion techniques used, the notes do not follow a consistent format. Items noted in bold, however, indicate that the discussion item was a key point from the breakout.

**A: EXPERIMENTAL DESIGN**

Objective

1. Overarching
2. Determine which population of TBI patients is most suitable for initial RCT study
3. Multi-Center Design?
4. Pre-Enrollment Screening/Evaluation and Inclusion
5. Population and Sample Size
6. Grant Funding Issues / Questions
7. Interim Analysis

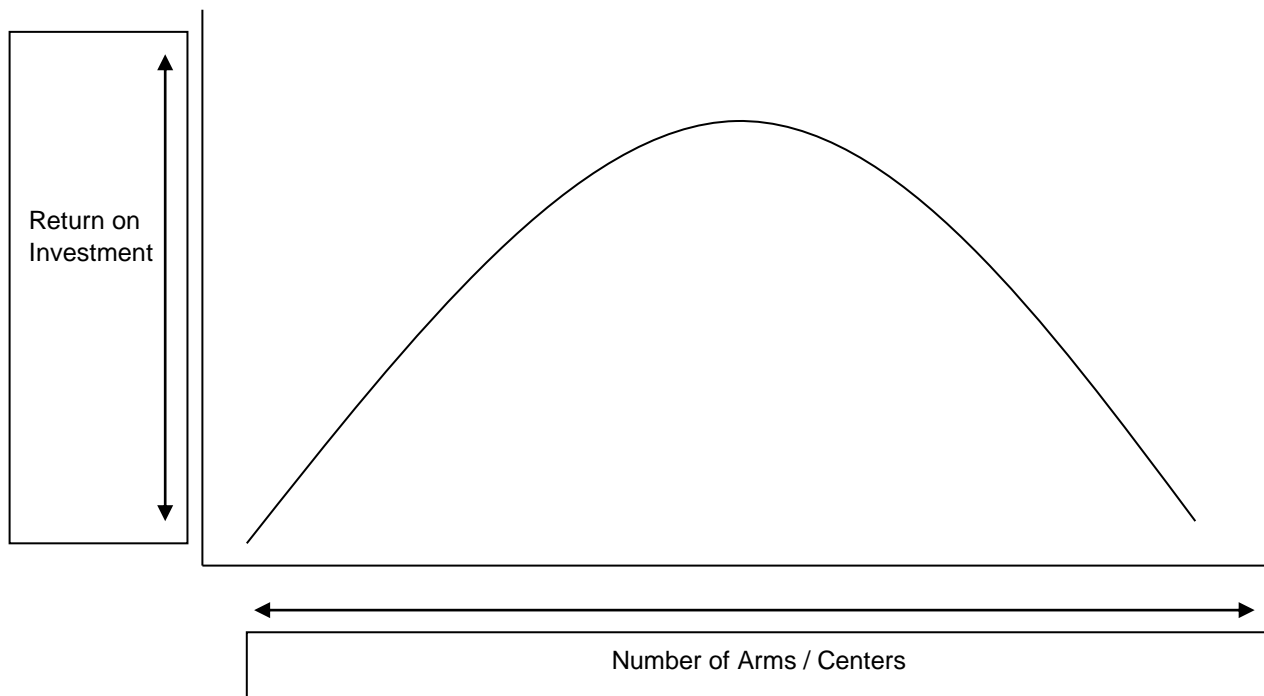
Parking Lot

- Development of PROTOCOLS for Dose, Severe TBI, Generalizability, Safety / Ethical
- Co-morbidity
- Analyze blast exposure versus mechanical injury

Participant List				
First Name	Last Name	Organization	Phone	Email
Louis	Antosek			
Rocco	Armonda			
COL Carl	Castro	X		
Dick	Clark	X		
LTC Austin	Chhoeau	X		
Tom	DeGraba	X		
CAPT Mark	Lyles	X		
Maria	Mouratidis	X		
Tom	Neumann	X		
Tom	Pierce	X		
Steve	Reimers	X		
RADM Dave	Smith	X		
CDR Cliff	Woodard (?)	X		
Steve	Xenakis	X		
Keith	Prusaczyk	X		

Breakout Notes

1. Introductions
2. Bringing the efforts of the Services together – maybe it's time to start putting all our eggs in one basket...if it's (the egg) worth it, and if it's a good basket
3. ANALOGY: We're not interested if the pathway of TBI is X, Y, or Z. We want to fix it.
  - a. ATOMIC BOMB: We didn't care how it worked or if it was an "efficient," sustained nuclear reaction, we just needed a bomb to end the war
4. No reason that a double-blind RTC cross-over clinical trial is not feasible – so EVERYONE gets treated.
  - a. We're not inventing hyperbaric oxygen therapy, though.
5. We're dealing with a medically stable population (same now as 3months out)
  - a. One group does nothing first; Other gets treatment
  - b. CROSS-OVER
  - c. Other group does nothing; Second group gets treatment
  - d. DISCUSSION: Sham treatments work
6. 1996: Six trials for HBO2 for CO poisoning (with fire victims – heterogeneous group). We faced many of the same problems at the time.
7. What is "Nice"/Wanted? versus What is Feasible?
  - a. Factors to be Considered
    - i. Variables...using the variables to help design the study
      1. Sensitivity of "Detectors"
      2. Variability of Testing
    - iii. Intervals of Observation...each 5 treatments, graded, what makes sense, what do the dynamics of HBOT dictate?
    - iv. Power 0.8 @  $\leq 0.05$



ii. Grade of Trauma/Disability

1. mTBI    Moderate    Severe    Penetrating
2. Age of Trauma (windows)
3. Acute                      Chronic
4. Feasibility of HBOT beyond acute phase
- iii. Type (including CONTROL group, blind group, ethics) and Frequency of Intervention  
Number of Intervention Cycles
- iv. Atmospheres (ATMs)
- v. Fraction of Inspired O<sub>2</sub> – we won't make this decision, but we'll have to address
- vi. Duration of "I" Primary Therapy
- vii. Dose – Response
- viii. "Imperfect" Model of Pharmaceutical Development DOES NOT Fully Apply  
[ 0, 0.3, 1.0, 3.0, 10, ... ] Stoichiometric basis for typical drug response  
But our "drug" is oxygen, and the "response" is not linear  
Ex. Response at 1.0atm is different than at 3.0atm
- b. Randomized Controlled Model
- c. Potential for Realizing this Goal at Multiple Centers
- d. Q: Does the group feel that the safety for HBOT patients is generally accepted?
- e. A: Especially at 1.5atm, safety of the treatment is not an issue. But we need appropriate training and certification.
  - i. This is a NEW INJURY, whose natural history is not well-understood.  
Outpatients don't always look like sports concussion injury.
- f. A: Overpressure injury (squeeze-and-release) is a different mechanism than Mechanical injury (crush).
- g. Q: What if someone commits suicide in one of the associated arms? In NEW DRUG testing, that would be a considerable red flag?
- h. A: Adverse events have to be reported and discussed.
- i. Q: If HBO<sub>2</sub> is considered a drug, what about DRUG INTERACTIONS
- j. A: No one is coming in clean. I suspect not, but there is no guarantee. And it is a significant concern. CONSIDER the elderly diabetic patient. This is why it needs to be a CONTROLLED TRIAL. Some issues will be psychological, some will be physical
8. AIR BLAST literature (10ms)
  - a. Hits lung wall where it hits
  - b. Squeezes chest inside
  - c. Rebound compressions
  - d. Presumed cause of prompt death is AIR EMBOLISM – but we don't know about those who don't die
  - e. Q (rhetorical): What is this group we're talking about? WHO are they? What are their SYMPTOMS? How do we say that we've IMPROVED THEIR QUALITY OF LIFE?
9. **ORDINAL PROBLEM: THERE IS NO VALIDATED DEFINITION OF mTBI**
  - a. TBI is a pathophysiology
    - i. Q: How many people already have these pathophysiological abnormalities?  
And how many people simply exposed to HBOT would show improvement?
    - ii. A: That's why it needs to be a double-blind crossover experiment.
    - iii. We have to have a DELIVERABLE and we have to have it FAST
10. **QUESTIONS WE NEED TO ANSWER:**
  - a. Q: Population: Mild and/or Moderate
  - b. A: "MILD" Definition – the hidden injury – makes it mysterious and scary

- i. Hard to differentiate between MILD and MODERATE: Needs to be a SYMPTOM-DRIVEN DEFINITION
- ii. Stratify Analysis
- c. Q: Which group is more likely to show us a DELTA?
- d. A: I suspect that those in the MILD are more likely to get better if you don't do anything.
  - i. "MILD" group is entirely TOO HETEROGENEOUS...you cannot group someone who was "dazed and confused" for 10 seconds with someone who had an LOC for 29 minutes – although BOTH are considered mild.
  - ii. RECOMMENDATION: Go for the most homogeneous group you can get (with a big "n") – where people are reporting good results – then we report to DoD on the largest generalizable groups
  - iii. CONTROL GROUP: soldiers in Iraq who've been injured, but not to the head
  - iv. Find the most homogeneous group and treat them all the same
  - v. Q: Is there a modal population
  - vi. A: Non-specific "Mild" with some combination of combination / cognitive / emotional (subjective complaints)
  - vii. We see Deficits in Attention and Spatial-Visual Skill, which is different from sports injuries
  - viii. Intervention – REMEMBER: **Risk / Benefit Ratio**

Ambient O2 \*  
ATM 1.0

Ambient O2 \*  
ATM 1.5

100% O2  
ATM 1.5

100% O2  
ATM 2.0

100% O2  
ATM 2.5

- ix. Q: Control or Comparison Group?
- x. A: Control group either has to be done AT PRESSURE done at regular pressure
- xi. Decompression Sickness becomes a problem with a Control at 2.0 atm
- xii. Q: Is dose-response the best way?
- xiii. Q: Is there a scientific basis for any particular dose?
- xiv. Q: What if the dose that we decide is "best" doesn't work? Best likelihood of success, but fails?
- xv. A: At least it provides a PROGRESS-ive answer

11. POINT: The number of treatments dictates the dose: **Haber's Rule/Law in Pharmacology**

12. STROKE Study – leukocyte blockage

- a. What we think happened: UP-regulated the immunologic response
- b. Q (rhetorical): What if it's reperfusion PLUS migration of progenitor cells?
- c. A: WITHOUT doing more than one dose, we won't be able to look at that
  - i. EX: Control      1.5ATM      2.0ATM

13. Information We Need to Receive from Other Groups:

- a. Number of Treatments      25      40      80
- b. Frequency of Treatment      1/day      2/day

- i. Pharmacokinetic
    - ii. Pharmacodynamic
  - c. Duration of Primary Therapy (Rx)
  - d. Age of Trauma (# of Traumatic Events) We suspect 6 months from trauma
    - i. Open-ended...Stratify
  - e. Age Group(s)
    - i.  $A \leq 30$  years > B Stratify
  - f. **And stratify by Sex in analysis – in fact, we should OVERSAMPLE for WOMEN**
  - g. Frequency of Data Collection – figured out by another group
  - h. **Interim Analysis and/or DSMB**  
([http://en.wikipedia.org/wiki/Data\\_monitoring\\_committees](http://en.wikipedia.org/wiki/Data_monitoring_committees))
- 14. **Agreement:** The **BLIND** aspect of this study is **ESSENTIAL**
- 15. Determination of which gaseous mixture and at which pressure of administration is up to another group, however it will be essential to ensure that the BLIND group doesn't know they are just that
- 16. TRUE Control is needed
- 17. Crossover study should be implemented to ensure that all participants receive treatment
- 18. LOC will be the standard criteria for inclusion (3% – 5% of those with TBI actually lost consciousness)
- 19. CONCERN: There was a cohort of patients who experienced head trauma WITHOUT Loss of Consciousness who still exhibited significant debilitation.
- 20. CONCERN: We cannot redefine mTBI ... need to use the classic definition. Clinical Practice Guidelines direct these diagnoses.
- 21. We need to move beyond diagnosis by symptoms and focus on functioning – the POWER of a TRULY DOUBLE-BLIND STUDY
- 22. Why don't we ask the HYPERBARICIST "What are the standard protocols?" and just go with that recommendation.
- 23. Dose = (Atmospheres) x (Time in Minutes)
- 24. Q: Does the FDA view HBOT as a drug or a device
  - a. HBO2 = Drug
  - b. Chamber = Device
  - c. When the two are combined, they (FDA) abides by the DRUG review process
- 25. Phase I / Phase II Trial - - Dose MUST be included, otherwise we're back to Phase I Trial
- 26. **AGREEMENT: on a Randomized, Blind,**
- 27. BLIND = everyone except the PATIENT and the adjudicator (EVALUATING PHYSICIAN)
  - a. \*\* The administering technicians and/or providers KNOW what they're doing
- 28. **Experience needs to be a consistent across treatment facilities: Mono-place vs. Multi-place Chamber, Hood, etc.**
- 29. The consulting pharmacologist can make the determinations as to 1.0 – 2.0
- 30. What are our questions, and what are the ways to find answers to those questions? We shouldn't throw it all into one study...
- 31. In the context of Legislative Directive to Treat; Congressionally-Appropriated Funding to Provide, EFFICACY is the ULTIMATE QUESTION – we need to be able to advise as to what is SAFE and what WORKS.
- 32. **We are trying to prove EFFICACY. How do we determine the efficacy of HBOT?**
- 33. **RECOMMENDATION to the Outcomes Group:** HEADACHE should be addressed as an outcome: Is this a Head Injury, Vascular Injury, Head-and-Vascular Injury Study
- 34. Headache is the only difference between mTBI and PATIENTSD
- 35. ?? **RECOMMENDATION to the Population Group:** Exposure to BLAST is a criteria...could also include mechanical

36. **DESIGN:**
- Prospective, Randomized, Double-Blind, Multicenter, Stratified [(A) ≤ 30 years > (B)] with a Parallel Group, Sham-Controlled
  - \*\* Open Label Extension Option?
  - Preference for a Data Safety Monitoring Board (DSMB) – should be required – and possibly also an interim analysis.
37. **QUESTION:** Crossover element? **Maintenance of true BLINDING delays** the time to when you can actually perform an analysis (i.e. **extends the duration of the full study**). What if we just allow those who were in the control group access into one of the TEST groups?
- You also lose the ability to follow-up...We probably want to maintain a 6-month follow-up (perhaps 12 months) before either crossover or admittance into treatment group**
  - Duration of Study is highly dependent on the SCALES that the OUTCOMES Group identifies**
  - Time is a Treatment (i.e. DISTANCE FROM INSULT)
38. **We need to develop a treatment protocol which closely resembles what they will receive in their respective community.**
- 5 days/week x 12 weeks = 60 SESSIONS
  - 3 days/week x 14 weeks = 42 SESSIONS
39. We don't want to exacerbate existing conditions: Human Safety, Concurrent Treatment of Medical Conditions, Structure
40. ETHICS: Can they truly consent? Can an individual with brain injury consent?
41. **GOAL for this study: Efficacy; and if we prove efficacy, then DOSE Response**
- Safety
  - Efficacy
  - Dose
  - Generalizability
42. There will have to be a post-hoc analysis to determine if there is a population that would've required a higher pressure
43. **What's happening at 3 months?**
- Some start to separate at 3 months
  - Some start to look better at 3 months (SEE: Dr. Mouratidis)
  - Some look exactly the same
  - Q: Is there going to be an achievable analysis in measuring end point between MILD and MODERATE?
  - A: I think that severe and moderate in this study will lead to significant confounding – it is a different protocol ... there will be too much noise
44. **POPULATION / PRE-ENROLLMENT SCREENING: Symptom-driven screening should be implemented as opposed to Diagnosis-driven**
45. **We need to stratify by FUNCTIONING / IMPAIRMENT**
46. POPULATION DEFINED via
- Symptomatology / Degree of Impairment
  - "Mild" / "Moderate" Satisfaction ...
47. SELECTION is based by WHO CAN COMPLETE THE ENTRANCE CRITERIA, regardless of symptoms
48. **Pre-Enrollment Screening / Evaluation / Inclusion**
- Ability to execute endpoint tests
  - Exposure to an external event
  - Mechanical

- d. Blast Overpressure
- e. Occurring in an individual “in-theater”
- f. Exclude (i) pre-qualifying injury occurring in the past, (ii) pre-existing seizure disorder, (iii) prior stroke, or (iv) other prior CNS pathology
- g. DEBATE WITHIN THE GROUP ON THIS POINT]
- h. Pregnancy or non-willingness to use adequate contraception

**49. Population / Sample Size**

**a. Determined by...**

- i. Endpoint “detector” sensitivity
- ii. Endpoint test internal variability
- iii.  $\Delta_{\min}$  (minimum change) of “clinical significance” for primary endpoint with a **Power of 0.80** and 95% Confidence ( **$p \leq 0.05$** )
- iv. Relative to primary stratification groups

**59. Intermediate Analysis? Perhaps, but DEFINITELY Data Safety Monitoring Board**

- a. Bayesian (sp?) Analysis

**B. PATIENT SELECTION AND END POINT ANALYSIS**

**Objective**

1. Ethical issues/questions
2. Military and civilian populations? Military only? Blast Only?
3. What psychological and neuropsychological (neurocognitive) tests are best suited to the chosen patient population and for statistical evaluation?
4. What evaluation methodologies are best suited to the chosen patient population? Exams, neuroimaging studies, lab studies, neurological, PM&R, psychiatric evaluation?
5. What analytical tools should be used to validate these findings?
6. Determine inclusion/exclusion criteria to develop highest specificity.
7. Include overlapping psychological/psychiatric co-morbid conditions? PATIENTSD, depression, etc.

**Parking Lot**

- Amputees and orthopedic injuries? b/c of altered Neurocog scores
- PATIENTSD –separate arms?
- Specific medications?
- Need to also look at combat other injury group to standardize for their problems?

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**Breakout Notes**

1. Introductions
2. Run down of goals (as above).
  - a. Q: Any other suggestions?
  - b. A: Dr French: What are we trying to study exactly? mTBI: most resolve regardless of treatment.
  - c. A: Smaller group has persistent symptoms that does not resolve as expected – so which group are we focusing on?
  - d. A: Dr. Weaver – focus is on those mTBI who do not resolve as expected, and how/when to study those
  - e. A: Lt Col DeJong – do this with focus on developing a potential study plan
  - f. A: Also should try to define multiple populations, time permitting

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- g. A: Dr. Weaver – easier to define those who do not resolve as expected and target for study population?
  - h. A: COL Bartoszek – No: those patients are least likely to benefit from HBOT or other treatments. Therefore better to look at mTBI, especially acute, and address outcomes and timeframes, etc.
  - i. A: Dr. Weaver -3 possible studies: acute, sub acute, late
  - j. A: COL Bartoszek –anecdotal evidence counts for nothing; these do not address placebo effect especially given the nature of the treatment.
  - k. A: Dr Weaver – given the types of patients, perhaps multiple studies are necessary
  - l. A: Dr Rockswold – acute is easiest to study for many reasons
  - m. A: Dr Weaver – Steering Committee is clear that acute is not the focus
  - n. A: COL Thurmond – intention is to address the questions regarding anecdotal evidence in the chronic TBI population (due to popular and political)
  - o. A: CDR Tsao – need double blind placebo controlled, ideally cross-over
  - p. A: Dr Weaver – while cross over does improve strength of study, it is not necessary given the clinical equipoise. It is/would be more for recruitment and political reasons.
  - q. A: COL Bartoszek – sham treatment NEEDS to be included in the trial. General agreement to this.
  - r. A: Dr Weaver – **agreement on chronic population?**
  - s. A: COL Farr – difference between shell shock in WWI and now, is that now patients have 24 hrs and 35,000ft while returning to CONUS. It is time for HBOT to get a good, strong, scientific study on the books.
  - t. A: Lt Col DeJong – study ongoing in rats regarding timing of MEDEVAC
3. COL Farr Recommend military only
- a. Discussion
    - i. Dr Pluth – if civilian population also have trouble translating to Blast population
    - ii. Dr Weaver - good to try to keep this as relatively simple as possible.
    - iii. Dr French – blast population also has other co morbid and unique features (polytraumas)
      - 1. However, blast patients could also have many confounding factors to muddy the results and analysis
    - iv. Dr Weaver – could stratify for blast cohort
    - v. Dr French –yes, no “pure” blast experience
      - 1. Maj Vogt – very difficult to say a patient has never had/had one/had many blast injuries
      - 2. Better to stratify for no blast/only blast
      - 3. COL Thurmond – don’t want to limit to ONLY blast, can analyze appropriately later
    - vi. Lt Col DeJong – collect mechanism of injury data and look at it later to address as an aside (possibly) does blast exist as a unique mechanism of injury
    - vii. General Agreement – blast and other mechanisms of TBI in a military population**
  - b. Q: Lt Col Stone – include AD, Guard, Reserve?
  - c. A: COL Farr – yes. If you go to war, you get to get hurt
  - d. Q: Maj Vogt – Who would be controls? Would we include noncombat (ie sports) related injuries?
  - e. A: Dr French – need to also look at combat other injury group to standardize for their problems?
4. Inclusion/Exclusion Criteria
- a. Q: Combat related only?

- b. A: Not only combat – many different injuries, in theater or out of, by many mechanisms
    - i. Lt Col DeJong – concern that the resulting study population would not be representative
    - ii. Dr Weaver – lets move to exclusion criteria to settle some of the questions
  - c. Discussion about when patients are beneficiaries to facilitate IRB approval etc.
  - d. Q: Dr. Weaver – don't we want to know in general if HBOT works?
  - e. A: Lt Col DeJong – need to have a population that answers the questions about patients whose injuries occurred in theater; including CONUS MVA's etc. might give non-generalizable results
    - i. COL Farr – So, needs to be in theater to address those questions.
    - ii. COL Thurmond – need is to be able to generalize across populations, and just looking at theater population will still give answers about whether HBOT works.
    - iii. DR French – DoD TBI population has not changed much over the last 15 years. IF you don't deploy people they will get TBI's in CONUS. Still important issue because it gets to the readiness of the force. So, a way to do it might be to organize people by symptomology
    - iv. COL Farr – if you include CONUS/Garrison population you'll get a preponderance of motorcycle MVA patients
    - v. Lt Col DeJong – focus, politically, is in theater populations
  - f. Q: COL Thurmond – but how do you define "in theater"? SPECOPS all over the place.
  - g. A: Dr Weaver – fundamental criterion needs to be that they had a documented TBI, and defining inclusion by symptomology would undercut that.
    - i. COL Thurmond – Use **terms "Deployed in support of OIF/OEF"**
    - ii. Group agreement
5. Define TBI
- a. Dr French – DoD/VA definition. Use mTBI classification (GCS = 14/15, LOC <30min, etc.)
    - i. Number of redundant screenings in DoD system
    - ii. COL Bartoszek – but Dx of TBI could and does change with each screening
  - b. Q: COL Thurmond – so how do you define chronicity
  - c. Q: Lt Col Stone – ICD-9 codes?
  - d. A: Dr French – DVBIC effort to organize codes but doesn't fix the fact that people don't code right
    - i. Dr\_\_\_ - Need to Address "where are they now?, what is their status now?" need to address force readiness
    - ii. Dr Langlois –need to start at least 3 months after injury to define chronicity
  - e. Q: COL Thurmond – can you pick people at 3, 6, 9 months?
  - f. A: Dr Weaver – yes, but this can compromise results
    - i. Dr French – cutoff time needs to be 3 months from most recent injury to pick up chronicity
    - ii. Also don't want to have to rely on proxy consent
    - iii. CAPT\_\_\_ - Need to narrow the window when most of these people resolve
  - g. Dr French – tricky issue because of development of comorbid mood disorders that when resolved, improve symptoms of the TBI. In these patients you don't know which you are treating.
    - i. Also potential iatrogenic effects of doing the treatment too soon
    - ii. Lt Col DeJong – also, many folks with other trauma injuries are full of other confounders (other surgeries, potential hypoxic incidents, etc), so I would say 6 months

- iii. COL Farr – also during that time, many people are out-processing, so you will need to address issues of secondary gain.
- iv. Dr Weaver – treatment takes approximately 3 months
- v. COL Bartoszek – so this straddles when people are leaving the military
- h. Q: Dr Pluth – what is the long term cut off/ceiling?
- i. A: Lt Col DeJong – even if people are far out post service, there will be a way for them to have access to HBOT equipment
- j. Q: COL Thurmond – can't you stratify for the variables we're talking about?
- k. A: CDR \_\_\_\_\_ - you would need to increase your N so much to address those
  - i. So there will need to be many studies to address all this
  - ii. You'll have to say "with this population, at this time, this is what we can say"
  - iii. COL Farr – the people bringing this to the forefront are those who are farther removed from the military, post discharge
- l. Q: Dr Weaver – so do you require them to be discharged and in the VA system?
- m. A: CDR \_\_\_\_\_ - No, but you need to define who the VA population is.
  - i. COL Thurmond – so say 'at least 1 year after separation and not undergoing a board'
  - ii. Lt Col DeJong – I still say 6 months because telling someone to wait 12 months while symptomatic because you don't have data is too long to wait
  - iii. COL Bartoszek – I agree. 6 months is good compromise time. 12 months is too long.
- n. **Q: Lt Col Stone – 6 months from Dx or 6 months from injury?**
- o. **A: Group – from injury**
- p. **Q: Dr Weaver – So consensus on 6 months and stratify?**
- q. **A: Group – you have to enforce the stratification**
- r. Q: Dr. Weaver – so what is the top end? 24 months?
- s. Q: COL Bartoszek – is anything going to work after 6 years on neurological injuries?
- t. A: Group – Only evidence about the long term is the largely anecdotal evidence from Dr Harch
  - i. DR Weaver – that is why we are here; higher ups are hearing this evidence
  - ii. COL Bartoszek – you don't want to prevent the study from working by recruiting people for whom nothing is going to work. So to what extent is it reasonable to liberalize time?
- u. Q: Major Vogt – sounds like money is not the issue, and number of patients is not the issue, why not do both?
- v. A: Dr Weaver - **study 6-12 months, 1yr-2 yr, 2 yrs to start of OEF, separately and simultaneously**
  - i. Dr Weaver – **time will have to be handled either factorially, or statistically. We will need to recruit proper expertise to handle this**
  - ii. Will need to include questions of number of blast injuries
- w. Q: Group: will we rely on theater documentation or self report for this?
- x. Q: Dr Weaver – Other inclusion criteria?
- y. Q: Col \_\_\_\_\_ - ability to document TBI?
- z. A: Dr. Puth – because theater records are inaccessible, you'll get self selection bias
  - i. COL Farr – won't have objective records unless you went to Level 3.
  - ii. Lt Col DeJong – many TBI will not even be reported at level 3 in theater. You need to have Physician dx at the 6 month point that says the pt is experiencing specific symptoms, etc.
  - iii. Q: Lt Col Stone – Should this be by referral?

- iv. A: Lt Col DeJong – theater data is available for many patients, so we should look at that, but the inability to get that should not be an exclusion criterion
- v. Q: Dr Weaver – so what are the rules we use?
- vi. A: COL Bartoszek – Somatic, Neurocognitive, Affective, Physical, etc
- vii. COL Thurmond – can use the symptoms in the DoD/VA definition
- viii. COL Baroszek – need some kind of brief neurocognitive testing that includes validity testing and that does not contaminate subsequent testing
- ix. Q: Col\_\_\_\_\_ - Can't you use baseline testing as an exclusion criterion?
- x. A: COL Bartoszek – use validity testing failure as exclusion criteria
- xi. Q: Dr Weaver –what about those who share with their friends the best way to fail the neurocognitive test?
- xii. Maj Vogt – You don't necessarily need to tell them why they are not being included if they fail
- xiii. Dr Langlois – Clinical interview is still the gold standard
- xiv. Group – yes, a clinical interview must be an inclusion criterion
- xv. Q: Dr Weaver – who does it?
- xvi. A: Dr Rockswold – Rehab group: physicians, neurologists, etc.
- xvii. Dr Langlois – so two options: either look for previous confirmed dx, or screening and interview
- aa. Col\_\_\_\_\_ - **participants need to be referred by a physician; those who self refer should be told to talk to physician at a specified small group of referring physicians who can then evaluate them**
  - i. **Dr Weaver – yes, but a clinical interview still needs to be part of the study**
  - ii. Dr Weaver – **Exclusions:**
    - 1. **Illicit drug use,**
    - 2. **alcoholics,**
    - 3. **claustrophobics**
- bb. **Any of the list of contra-indications to HBOT**
  - i. Group: alcoholics as outliers, abuse vs chronic alcoholics
  - ii. Maj Vogt – Add another - PTSD without TBI arm?
  - iii. Group – no would require the study size to be too large
  - iv. DR Weaver – Obviously exclude for:
    - 1. **Pregnancy**
    - 2. **HBOT Risk: chronic stable heart failure, bolus emphysema, other standard HBOT exclusions, claustrophobia,**
    - 3. **history of brain surgery**
    - 4. **psychotic disorders**
    - 5. **other neurologic disorders in past, especially demyelenating, hypoxia, CVA, meningitis, seizure disorders, past history of severe head injury (other than the one for which they are being treated)**
    - 6. **Control for multiple concussions, but don't exclude**
    - 7. **Prior HBOT treatment for other injuries or diving related problems**
    - 8. **Cerebral DCS**
    - 9. **PATIENTSD should fallout In the balance, so no need for separate arm**
    - 10. **Any serious clinical manifestation a responsible screener believes should be exclusive (ie liver failure, malignancy, etc)**
    - 11. **Amputees**
  - v. Dr Weaver – Include all comers seems to be the new task

- vi. Maj Vogt – Talking with Dr Harch, he brought up the point that a cross over would make it difficult to know how long the effects of the treatment would persist, which would undermine the study.
- vii. COL Farr – it is better to offer those in the sham group an opportunity for treatment at a later time. This is already too complicated
- viii. DR Weaver – treatment protocol is already likely to be very long
- ix. Lt Col Stone – because you would want long term follow up of the control group as well. Minimum one year
- x. Lt Col DeJong – we do not want to feed into the stereotype that medical research takes too long.
- xi. COL Thurmond – next studies, subsequent studies would be able to address some of the other questions we are discovering
  - 1. Q: How long would it take to get patients enrolled and get data
  - 2. A: Dr Weaver – due to all the needs of this, you will limit the number of chambers that are available: you can't use all the chambers in the country because they lack the appropriate research community and infrastructure in many cases. Could get this be done in 2 years
- xii. COL Farr – people are just worried about sample size, which will likely not be a true problem.
- xiii. Col Maher – important question would be whether you increase the number of chambers you can access, or make academic institutions more robust
- cc. Dr Weaver – again, talk about including all comers: Mild TBI to Severe
  - i. Q: What does Severe mean? Vegetative?
  - ii. A: Lt Col DeJong – yes because the talk was about patient inability to complete in assessments, etc other than neurological exam
  - iii. COL Thurmond – makes the study too complicated
  - iv. Dr Pluth – would make it too complicated, and as a result you would not be able to compare across groups anyway
- dd. [sidebar discussion of proposed/hypothesized mechanism of action]
  - i. To address this question of mechanism of action you would need to have NIH involved to do longer more involved studies
  - ii. As of now it is a black box treatments of an ill defined disease
  - iii. We are at a point where we need to take fine, concise, measurements of patients in an open study design to discover where the data are headed, not just where they are, and then you use that to dictate your next study
  - iv. What we are talking about here are biomarkers
  - v. A good strategy would be to use the best possible neuroimaging, and microarrays to look for everything and the kitchen sink even if just in a smaller cohort (Nick's word choice)
- 6. Dr Weaver – All Comers:
  - a. COL Thurmond – lets list inclusion/exclusion criteria for each of the categories
    - i. Dr Weaver – good idea, but need to define what is mild vs moderate. Severe is easier to define
    - ii. Lt Col DeJong – there will be a confluence of mild and moderate at the 6 month time point. So do we classify them as mild/moderate based on initial injury or at time of inclusion
    - iii. Maj Vogt – need to go with initial injury because we are not clear about why a mild TBI has sx similar to those of a Severe TBI 6 months later
    - iv. Col \_\_\_ - play devil's advocate and say include only moderate to severe because improvements will be more marked and will be easier to define in the

- VA population for the sake of benefits, etc. Furthermore, in mTBI there are many questions about comorbid PATIENTSD the sx of which are difficult to tease out.
- v. Dr Weaver – you can either include them as a separate group, or do a separate study for them
    1. So here at the 6 month point, how do you define these groups?
  - vi. COL Thurmond and Dr Weaver – at the point of enrolment you need parity to be able to compare results, so wouldn't you want to include severe injuries, but who are screening at a mild level?
  - vii. Lt Col DeJong – but because of the “long road” and drastic improvements of a severe who has improved that much, how much room is left/possible for them to continue to improve?
  - viii. Dr M\_\_\_\_\_ - you need to consider the heterogeneity of the initial injury
  - ix. COL - Include all comers, do comprehensive and widespread screening and assessments of what is going on and do the analysis later. Maybe the result would be that mild/moderate/severe is not a predictor of outcome.
- b. Q: Maj Vogt – why can't you have multiple concurrent studies?
  - c. A: COL Macedonia - Exclusion criterion should be that patients must be able to self enroll. Therefore vegetative state should not be enrolled.
    - i. Col \_\_\_\_\_ - Moderate population are more heterogeneous and that ability will vary.
      1. Could base this on an inclusion criterion that the medical record establishes whether the pt is capable of consenting
      - ii. Dr Weaver – it might not matter whether you had mild/moderate and are now screening mild if you can find a way to balance these people who are outliers
  - d. Q: COL Thurmond – would you give me different treatments if I were screening mild even though I had a moderate?
  - e. A: Maj Vogt – it depends on the patient. Deficits are very unique to the patient; someone who originally functioned at a very high level may screen normal, but that is still a huge deficit.
    - i. Dr Pluth – if you want this to be comparable to other TBI studies, you will have to base it on categorization at time of injury. Maybe you need 3 separate studies, with 3 sets of outcome measures.
  - f. Q: Col \_\_\_\_\_ - It is the anecdotal evidence of the moderate/severe that are largely driving this politically?
  - g. A: COL Macedonia – disagree; it's the milds for whom nothing else has worked and who are lucid enough to figure out something is going on
    - i. So the imperative is to figure out a way forward to discover whether this does work; get our arms around anything and everything that might be able to give relief to patients; command does not want to micromanage
    - ii. **COL Macedonia – rebuttal to criticisms about excluding severes / those who cannot enroll themselves is that we need to define efficacy before taking the risk of enrolling them – to protect these patients**
    - iii. COL Thurmond – exclusion criterion needs to be that pt must self consent
      1. Clinician will also be signing off that due diligence has been done for this individual
  - h. **Conclusion: all chronic TBI, not just mild, that can self-consent**
7. Q: What are Referral criteria? Refractory to treatment?
  8. A: Maj Vogt – they don't have to have tried anything.
  9. A: Dr Pluth – can analyze other treatments after the fact

10. PATIENTS

- a. Control for them. Measure on entry and at conclusion; not separate arm.

11. Exclusion Criterion – CVA should be PHx unrelated to the TBI (Maj Vogt)

12. Q: Seizures – Same reasoning as for excluding those not able to consent themselves – to protect them?

- a. Need to analyze incident seizures during the treatment protocol, even though these patients may need to be pulled from intervention due to the fact that you cannot say the seizures were caused by HBOT or not
- b. Incidence of seizures in severe TBI population is approximately 20-30%
- c. Maj Vogt – another issue is the role of anti-seizure meds
- d. Col\_\_\_ - removing seizure patients would weight toward mild
- e. Starting seizure meds around the same time will bias the HBOT outcome
- f. COL Farr - Someone will have their first seizure in the Chamber, based on the amount of time they are in the chamber and the incidence rate. Need to prepare for that.
- g. COL Maher – Exclude epilepsy
  - i. Dr Weaver – Dr Harch will say that it is irresponsible to use a pressure above 1.5 ata because it will provoke seizures.
- h. Group agreement to use Epilepsy as an exclusion criterion

13. Drug and Alcohol Confounders

- a. Q: Lt Col Stone – What drugs are we talking about?
- b. A: Dr Weaver – **illicit drugs**, but how will you know?
  - i. COL Macedonia – Scientifically cant allow them because they confound result
  - ii. Tobacco? – Dr Weaver: in wound care they need more treatment
    - 1. **Stratify for tobacco use**, not exclude. Should be prevalent enough that it balances out in randomization
- c. Q: Alcohol? CNS effects of chronic alcoholism, physiological, psychosocial, need to be addressed as they can be confounders
- d. A: COL Macedonia – could discover that outcomes improve because use of mind altering drug use decreases
  - i. Can measure tobacco, alcohol, caffeine use and are prevalent enough that you need to look at them
  - ii. More difficult to control for illicit drug use
- e. Lt Col DeJong – need to also be sure that you are looking at a clean dx of mTBI, and not undiagnosed alcoholism, depression, etc., or convenient dx

14. Need thorough screening to define their injury: how, when, severity, LOC, etc. Even if just for the sake of recording

- a. Could also look at patients who have documentation vs those who don't
- b. Enables a qualitative decision to be made as to whether or not to include them.
- c. COL Farr – need a way to vet or throw out patients who claim that they can't say how/when/etc they were injured
- d. COL Macedonia – will be frauds and those with Munchausen, but these should fall out during analysis b/c of convergent validity of the rest of the sample
  - i. However, it is worth while to look at service records
- e. COL Farr – DD214 to prove discharge

15. Return to Drugs:

- a. COL Farr – test for illicit drugs and exclude
- b. Q: Lt Col Stone – but you would also need to test for prescription abuse and huffing, etc. Where do you draw the line?
- c. A: COL Macedonia – you need to exclude these people for cleanliness of the study
  - i. Alcohol and tobacco are ubiquitous enough that you need to include them

- ii. Cannot exclude people on prescriptions because you don't want to cause people to go off their meds to be included in the study. SO you need to screen for and analyze for them.
    - d. Q: Dr Weaver – do you report results of drug screens?
    - e. A: COL Farr – you will have to report positive screens for AD.
    - f. Q: COL Thurmond – can you just base this on self report?
    - g. A: Maj Vogt – what do you lose by screening for drug use?
      - i. Dr Weaver – drug screens and self report are unreliable. You're likely only discover marijuana
    - h. Q: Lt Col Stone – what about people in treatment programs
    - i. A: Dr Weaver – this is probably prevalent enough that it balances with randomization
      - i. Lt Col DeJong – but this begs the question, how do we know that the dx is accurate for TBI, and not just misdiagnosed (missed) drug abuse/alcoholism?
      - ii. COL Thurmond, you will have to standardize, train and oversee the clinicians doing the interview. Also do inter-rater reliability. So you'd have to analyze drug use in the end.
    - j. Q: Lt Col Stone – are there any contraindicated drugs for HBOT?
    - k. A: Dr Weaver – no, but cocaine and methamphetamines taken immediately prior to treatments may increase seizure risk
      - i. Would need patients to report any/all medications and illicit substances
    - l. Group: **NOT excluding alcohol and/or drug use**. Not going to directly ask but will ask “have you taken anything other than....”?
      - i. Dr Weaver – standard interview prior to every treatment session
16. Psychotic Disorders
- a. Q: Lt Col Stone – is there an increased risk for psychotic break in the chamber?
  - b. A: Col\_\_\_\_\_ - could relegate this to being up to the screener to make a judgement call
  - c. Dr Weaver – what if the psychosis is related to TBI?
    - i. **As long as they are not actively psychotic, there is no reason to exclude**
17. Amputees
- a. Q: Why not include? – Altered circuitry/tractography
  - b. **A: Dr Weaver, others – need to stratify but include**
18. Age – include all, but need to stratify
- a. Stratify at what age groupings still need to be determined??

**C. OUTCOME MEASURES**

**Objectives**

1. What are the neuropsychological outcomes that need to be incorporated in the study?
2. What neuropsychological test battery can be used to assess cognitive functions?
3. Who will perform the assessments?
4. What are the time points of assessments?
5. Does neuroradiography have value in our determination?
6. What imaging study do we suggest?

**Parking Lot**

- Outcome Measure: Brainchecker and IMPACT Measure
- Genetic - single markers such as APOE as response to recovery
- Hypothalamic- pituitary function

<b>Participant List</b>				
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## Breakout Notes

### Added discussion objectives

1. Symptom measures- discussed in the context of outcomes
2. Complaint of headaches is known; headache intensity
3. Polysymptom
4. Rivermead
5. Pain intensity scale
6. McGill Pain scale
7. Functional measure
8. Ecological Outcomes
9. Emotional dysregulation
10. Alcohol use disorder test- Audit C
11. Drug Abuse screen test
12. Urinalysis- drug screen
13. OQ45- life distress test
14. PCL-M- PATIENTSD Check list - military version
15. Impact and event stress test- IESR

### 1. Focus Outcome

#### A: Discussion

- i. **Chronic mTBI- GCS >13**
  - ii. **Not focusing on acute**
  - iii. **Chronic definition: 90 days or >; not capping the extension period**
  - iv. **Can be alteration of consciousness up to unconsciousness**
  - b. Q: Are LOC (loss of consciousness), PTA and GCS independent of each other?
  - c. Q: What are the assessment tools?
2. People should be better in weeks rather than months
  3. Neuropsychological testing is normal, job performance is significantly impaired and family interactions severely impaired
    - a. Discussion
      - i. Biggest change in emotional mobility
      - ii. Comes out in their job performance- not that they can't do it, but that they can't tolerate it
      - iii. Use surrogates because don't have a good measure point with spouses- self medicate with alcohol and drug use
    - b. Q: What is the clinical presentation that we are faced with where we think can most be impacted by HBOT?
      - i. Taking a step away from brain function and moving towards life function.
      - ii. One of the reasons to focus on these things is that people are looking for improvements in these areas and want that from HBOT.
      - iii. Adding noise to measure with life functions- spousal example- getting along with wife
    - c. Q: If dealing with indirect measures, why shouldn't we concentrate on ecological as being a therapeutic efficacy measure?
      - i. Most common complaints - emotional, sleep, headaches- need to make sure we have strong outcome measures that evaluate those 3
      - ii. Complaint of memory loss is subjective- if test people who say have memory problems; correlation is about .1

- d. Q: Do you see clinically significant change after intervention?
  - e. A: That's why we are here, we don't have a great intervention
  - f. Q: If treat b/c of complaints, do we see improvement on that same test?
  - g. A: We don't know the answer; we don't have group data either
  - h. Q: Where you do see change on improvement is on the subject of complaints
    - i. Speeding up information processing- can we concentrate on? - executive functions; memory is not an executive function. If test discretely you are going to miss memory
    - ii. Executive functions is so broad- all of our executive measures are timed, but speed is not an executive measure
4. Metronome training/therapy- how difficult it is to establish a learning curve- took test and supposed to go through training and had to re-test b/c too busy. Didn't have learning curve on test. Can train rapidly on it, but don't see dramatic changes on first round. Very difficult test. Daughter trains people on it and looked at images on people. It is a computerized test and the person who has done the best on the test are pilots. It is a speed and reaction test. It is a computer program where you have visual and audio cues. You want to clap at the same time as the visual and audio cues. They change it so that you learn to the rhythms. Is it validated? Who is it validated on? Don't have that information? It is a standardized test- very objective measure on response. If did test, you get the hyperbaric on individuals and then re-test and get enough body of information. Mentioned b/c really difficult initial learning curve. Standard training is 1 hour day for several days.
- i. If not validated research tool- not something we can stand on
  - ii. Looking at measure to modify behavior to other cues
- 5. There should be a breakdown of things in which are primary vs. secondary**
- a. The fact that someone complains less- you just get used to things- guy adapts to new level of functioning
    - i. People around them get used to it as well and don't complain
    - ii. If want to do with control group- to show difference
    - iii. Less complaining has nothing to do with hyperbaric oxygen
  - b. Literature shows there are not differences
    - i. have control group and mild TBI
    - ii. after 30 days no difference between matched controls and mild TBI
    - iii. 3 medical analyses that have been done
    - iv. whole point of experiment is to see if improvement
  - c. One objective measurement would be some of the testing available in balance centers
    - i. Validated
    - ii. Testing available
    - iii. And is stressor
  - d. Asked to do higher level of balance test- show weakness and deficit; very few complain and get vestibular
    - i. Vision testing
    - ii. Eye movement test that is subjective and sensitive
    - iii. Depth perceptions
  - e. Niastagmous test
    - i. Measurable
    - ii. Abnormal in population
6. There are subtle differences that neuropsychological tests aren't picking up
7. Will receive criticism b/c few people complain about balance problems
8. Tests mentioned have some of the longest tracks in the brain
- 9. Test for audiology on individuals**

- a. Discussion
    - i. Reason is single most abnormal test is the auditory processing where there is the auditory fMRI
    - ii. There is the objective correlate
    - iii. There is a tremendous amount of auditory dysfunction- use it as a measure to determine if can go back to work
    - iv. Have to have audiology to know if they are hearing and need to correlate with fMRI
    - v. Only time see ear not respond is b/c there is a peripheral hearing loss
    - vi. b/c high incidence of hearing loss- would need to be controlled in control group
    - vii. Cheap, fast easy test
    - viii. It is also subjective
  - b. Military is hesitant to look at audiology b/c of certain injuries
    - i. Blast injuries and hearing loss but if have objective measure could give you objective information
10. Objective test:
- a. Discussion
    - i. Balance
    - ii. Depth perceptions
    - iii. Eye movements
    - iv. Audiology hearing
11. PATIENTSD patients have alterations in audiology processing- common denominator is found in fMRI- focusing on system gives objectivity
12. Are there any other stress tests?
- a. Discussion
    - i. Hypoxia could be a stressor
    - ii. Just going into a chamber is a stressor
    - iii. Most people have PATIENTSD- no escape route
13. Marine corps culture has changed- it is now taught in officer school- if you are broke it is not a shame
- i. Won't have an issue in getting numbers; highly motivated
14. Emotional stress test- conceptually good idea
- i. Emotional stroup test
15. Are we looking for outcome measures for mTBI and PATIENTSD? Are we accounting for patients in both?
- a. Discussion
    - i. Do you want a PATIENTSD measure as an outcome? Or a covariate?
    - ii. Symptoms are making them dysfunctional and our outcome needs to pick it up
    - iii. Needs to determine if treating mTBI, PATIENTSD or both
    - iv. Searched high and low and don't know how to separate
    - v. Would also include depression with PATIENTSD- psychiatric co-morbidity
    - vi. Diagnostic criteria and significance
16. Primary Objective Biological outcome (mTBI):
- a. Discussion
    - i. (Neurobiological outcome) High level balance activity
      - 1. Neuropound
      - 2. Balance master
      - 3. Cairns machine

- ii. **Neurobehavioral Symptom Inventory (NSI)**
  - iii. **Neuroradiological**
  - iv. **Perfusion**
  - v. **Objectives or outcome measures are things at the end of the study and we should measure at the beginning of the study as well**
  - vi. Objective of group is to get outcome measures down and structure better tomorrow
- b. Q: Are there certain axes or factors we should look at for study?
- c. Difficult part of capturing brain injury- you often don't know where to start- which measure do you choose?
- 17. Brain perfusion- most sensitive b/c looking for change; structural changes may exist, but have not been well documented.
  - a. Discussion
    - i. Region of interest
    - ii. Focused on corpus colosum
    - iii. Next focus is hippocampus
- 18. fMRI paradigm- significant changes in motor and auditory; motor unusual; auditory more common
- 19. Imaging for structural defects in mTBI- not a lot of testing available; not severe injuries that usually show
  - i. All of the things that are not typically shown
- 20. Available of whole brain perfusion- not available to everyone
- 21. DTI can be quantified
  - i. Would be read centrally
  - ii. Brecher study- marines and army specific folks with breached doors and stand so many feet back- study done in Quantico- looked at Anam
- 22. Need instrument that captures ecological measures
  - a. Discussion
    - i. Measures with relationship satisfaction
    - ii. Need to have checklist that everyone puts into a common database
    - iii. Rating may correlate with outcome
- 23. Primary Objective Ecological Outcomes (mTBI):**
  - a. Discussion
    - i. **NSI (Neurobehavior Symptom Inventory)**
    - ii. **OQ-45- series of questions about how functioning in life- includes some mental health; self report measure of state stress**
- 24. Primary Objective Function Measure Outcomes (mTBI):**
  - a. Discussion
    - i. **Driving Simulation (decided not to include)**
    - ii. **Neuropsychology testing**
    - iii. **Sustained attention concentration- TOVA test (decided not to include- moved to secondary)**
    - iv. **Head to Head result giving direction**
    - v. **ANAM IV + imPACT test**
  - b. Q: What is an adaptive response to reintegration into the community?
  - c. A: Disequilibrium between family and community
  - d. Q: Is there a correlation with HBOT?
  - e. A: Would likely need a series of tests b/c not one test that covers all
- 25. Driving test measures a lot of things- driving simulator
  - a. Discussion

- i. \$70,000 to get small driving unit
- ii. Common in rehab hospitals
- iii. Military driving is different than community and is non-applicable to community driving
- b. Q: Why aren't continuous performance tests different in mild to chronic phases in mTBI?
- c. A: Easy to correlate tests with other bigger, larger tests that are ongoing

**26. Q: Should the ANAM be part of the study?**

**A: Doing it now is useful b/c that is what military is using**

- i. **Getting the process down is horrendous**
- ii. **Validated test within the military population**
- iii. Data we know on ANAM that military is not sensitive to ANAM
- iv. Use it for face validity
- v. Pair ANAM with impACT

**D. HYPERBARIC TREATMENT PROTOCOL**

**Objectives**

1. What are the treatment protocols that should be used? 1.5 ata, 2.4 ata??
2. How would sham treatment be designed? Mixed gas, low pressure only?
3. Are these protocols safe?
4. Can we establish a dose effect curve? Multiple arms?

**Parking Lot**

- Need to look at how to create the most effective Shams
- Need to create a standard pre and post treatment checklist

Participant List				
First Name	Last Name	Organization	Phone	Email
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James	Kelly			
Mark	Olesen			
Fritz	Kass			
Mark	Llwewllyn			
Gaylan	Rockwold			
Anne	Helms			
Gustavo	Roman			
Frank	Butler			
William (Bill)	Duncan			

**Breakout Notes**

1. CAPTAIN HART AND DR GESELL OPENS UP WITH GROUND RULES, PARKING LOT, AND AGENDA FOR THE SESSION
2. Introductions around the room
3. Ground Rules discussed by CAPT Hart
4. Objectives discussed by Dr. Gesell
5. Additional topics
  - b. How many arms do we want? - how do we solidify dose response
  - c. How we do address pressure depth? - hi pressure, low pressure, acute vs. chronic

This information has been prepared solely for the use and benefit of the Defense Centers of Excellence (DCoE) and the US Government and is not intended for reliance by any other person.

- d. Do want to add airbrakes?
  - i. Number
  - ii. How long do we want these airbrakes to occur
- e. Duration?
  - i. 60 min
  - ii. 90 min
  - iii. 120 min
- f. # of treatments
  - i. Total
  - ii. # Per week (5-7)?
  - iii. # missed treatments, will they be excluded from protocol and how do we address that
- g. If complications, remove from protocol or how do we modify treatments
- h. Are we going to have standardized prophylactic for HBOT to lower risk for seizures (ie: anticonvulsants, benzo)
- i. Timing of Treatments
- j. Do they get evaluated fully daily, weekly?
- k. Patient screening
  - i. CXR, CT, ER
- l. Monitoring during HBOT
- m. Follow-up of patients
- n. How do we define treatment time (clock start/stop time)
  - i. Example: Hatch to hatch
- o. What is the change to the protocol to how the patient is doing?
  - i. Response: how do you do that in a sham study?
  - ii. Action is to eliminate changing the protocol because it's a blinded study
- p. Q: Does the size of the chamber matter?
  - i. A: No, as long as it's an FDA approved chamber
  - ii. Response - need to take into "placebo effect"
  - iii. Action: important to have shams to reduce variability in different location, chamber sizes, socialization effects
- q. Sham treatment is to give them boost and then drift down to give them depth sensation in monoplace treatments
- 6. Discussion of topics begin
  - a. What types of treatments do we want to use? What are the thoughts to the group (Dr. Hart)
    - i. **Might want two doses and a control because you want a dose effect that is verified against placebo treatment**
    - ii. Q: What are we trying to do with the doses? (Dr. Rockswold)
    - iii. A: We want to include 1.5 ata that is studied from other literature
    - iv. Q: Do we pick both ends of the spectrum?
    - v. A: 2.5 is superior than 1.5 in animal studies
    - vi. A: In humans 2.5 doses have shown higher risk of seizure rate. Do not see a reason to go high dose safely (Dr. Harch)
    - vii. **A: What we don't want to do is to leave the higher dose as a open question if we do not study higher doses.**
    - viii. **A: There are data on treatment to 2.5 ata that have not shown seizures (Dr. Gesell)**
    - ix. A: **Recommend include a placebo group, 1.5 ata, and 2.5 ata group**

1. Data shows that it is rare to show seizure at 2.5 from dive treatment data
  - x. We need to define dose response to how many vs. what ata
  - xi. **Q: Do we have to measure oxygenation**
  - xii. **A: Currently not a good measure to study oxygenation to the brain**
  - xiii. **A: It is tricky to collect this data**
  - xiv. **Q: Is the purpose to outline the objectives to one study or should this be two studies - one at 1.5 ata and one at 2.5 ata:**
  - xv. **A: Potential credibility of having two separate studies may arise if two separate studies are conducted so no to two separate studies**
  - xvi. A: There is an urgency to do the study so recommend not to study higher ata (Dr. Harch)
  - xvii. Resource are estimated to be approx 100 per arm
    1. **Power needs to be 686 units per pressure to have successful study**
    2. **Has to be done in the same study (Dr. Rockswold)**
  - xviii. **We need to define what constitutes significant difference**
  - xix. **Do not need to do multiple arms - all agrees**
  - xx. Decide on the design to be Sham, 1.5, either 2.0 or 2.4 or 2.5
  - xxi. Q: Has 2.0 has been treated as the lower starting doses
  - xxii. A: Yes, because it increases safety and don't need airbrakes
  - xxiii. A: Studies have shown that 2.5 is better than 2.0 in treating angiogenesis (Dr. Gesell) but 2.0 is used for safety to start
  - xxiv. **No one interested in 1.7 ata**
  - xxv. Clear difference in 1.8 ata and 2.0 ata in radiation neuropathy
  - xxvi. **One type of sham - all agreed**
  - xxvii. Why not conduct 1.5, 2.0, 2.5 ata arms?
  - xxviii. Response by Dr. Rockswold: "That will be a huge study"
  - xxix. Sham, 1.5, 2.0, 2.5 ata
  - xxx. Nothing in literature to support safety issues at 2.5 ata
  - xxxi. Do not want to create protocol to interrupt procedure if adverse symptoms are present at higher ata
  - xxxii. If 2.5 ata shows seizures, then that arm has to be eliminated
  - xxxiii. Would like more points to show potentially non linear
  - xxxiv. Sham, 1.5, 2.0, 2.5 is agreed for dose response protocol (REVOTE was done in Day 2.... LOOK BELOW FOR THIS DECISION)

## 7. Switched topics to how long duration of airbrakes

- a. 1.5 ata for 90 minutes?
- b. Dr. Harch says that 90 minutes you start to break down phasal.....
- c. Dr. Rockswold doesn't think there is real evidence of that deep oxygen therapy has positive effects. Need to be careful
- d. Treatment time has to be the same for all of the arms
- e. Q: Is there evidence that we can point to?
- f. **A: We don't know for sure with mild TBI (Dr. Rockswold)... there is a downside for too much oxygen but not proven.**
- g. **Need to consider safe practice first**
- h. Q: Are there negatives with going longer than 60 minutes per treatment?
- i. **Voting on 60, 90, 120 minutes per each treatment**
  - xxxv. **11 votes for 60 min - All agreed**
    - i. 0 for 120 min
    - ii. 0 for 90 min

## 8. How many airbrakes

- a. Q: Are going to blind the techs
- b. A: WE can blind the techs
- c. **Q: Can we go 2.5 ata for 60 minutes without airbrakes?**
- d. **A: Concerns is that there are much higher potential for airbrakes**
- e. **Q: What is the seizure risk at 60 min at 2.5 ata**
- f. **A: Don't know**
- g. **Q: If the literature shows that there is no evidence, then why airbrake?**
- h. **A: Dr. Gesell notes that she doesn't know of any protocol that doesn't airbrake at 2.5 ata - asking for trouble if we don't do airbrake at 2.5 ata**
- i. **Q: Is there a way to do an airbrake as a sham airbrake to prevent socialization effect?**
- j. **A: Just need an external tank to give them 100% oxygen for the airbrake.... Yes it is possible. Faking airbrake is reasonable at lower ata treatments.**
- k. Q: Will the time added for the sham to be noticed in outcomes?
- l. A: (not answered by group)
- m. You're changing the 1.5 ata 60 minutes, there is no evidence because none has been done before (Dr. Rockswold)
- n. Experience shows that a 5 min airbrake negates the effect of HBOT
  - i. But can't be compared, there are no comparable examples
- o. **Q: Are we going to damage people without giving an airbrake**
- p. **A: Yes, many will seize**
- q. Q: Does extending the treatment to 65 minutes violate the treatment
- r. **A: Need to have same protocols for all 4 arms**
- s. A: For two arms at 5 minutes less oxygen at 15 and 2.0 ata
- t. **NO AIRBRAKE during treatment - All Agreed**

## 9. When do we want to start the clock

- a. Start the study clock to Begin at depth to end of depth in monoplace
- b. **Need to consider patient perception**
- c. Compression and decompression needs to be slow to be consistent at all 4 arms
- d. **Dr. Harch does 60 minutes hatch to hatch so oxygen exposure is different at different ata**
- e. **Monoplace and multiplace chambers needs to have different start times**
- f. **Multiplace vs. Monoplace debate**
  - i. **Consider reducing variability by choosing either multiplace or monoplace**
- g. Q: Can we design a study that has the consistent compression and decompression?
- h. A: Throw in air compression lessons to show them how to equalize their ears
- i. CDR Kass suggests not to deviate from Dr. Harche's design to start as baseline
- j. Dr. Rockswold recommends eliminating 2.5 ata
- k. CAPT Hart says eliminating 2.5 ata will eliminate possibility of oxygen toxicity and will simplify the study and reduce noise
- l. Dr. Rockswold - safety is a major issue and 2.5 ata should be eliminated
- m. Dr. Helms says that FDA guidelines states that we need to find dose before efficacy so we need to look at 2.5 ata
- n. Getting back to the basic questions.. **How many arms study should we have?**
  - i. Sham, 1.5 only? 2 votes
  - ii. **Sham, 1.5, 2.0 8 votes**
  - iii. Sham, 1.5, 2.0, 2.5 3 votes
  - iv. Sham, 1.5, 2.5 0 votes

## 10. REVISIT When do we want to start the clock

- a. Multiplace and monoplace debate
- b. We have to have time for multiplace studies
- c. Average decent and assent time is 5- 7 minutes - Dr. Harch
- d. 50 minutes at depth is comparable in a multiplace chamber to hatch to hatch 60 minutes in monoplace chamber - CDR Kass asks for confirmation from Dr. Hatch and Dr. Hatch confirms - "roughly"
- e. How many are compressing and decompress having different between mono and multi
- f. **Everyone is comfortable with slight difference in comp and decomp differences**
- g. **Is 60 minute of oxygen the time at depth the right time for monoplace? All Agreed**
  - i. **multi place - oxygen (60 min) clock will start at end of compression**
  - ii. **mono - hatch to hatch - 60 minute clock starts**

**11. Total # of treatments.**

- a. 40 treatments is standard treatments for other chronic disease treatment types
- b. Dr. Harch has had experience with 40 treatment and 80 treatments
- c. CAPT Hart says we need a min and max threshold for treatment
- d. We should have a block of maybe 20 treatments with a min of 40 and max of 80
- e. We need a standard - do interim analysis and do assessments at some kind from 20, 40, 80...
- f. What are the constraints?
- g. **Is there any known data that supports potential toxicity after initial 40 treatments**
- h. **Dr. Harch - no data that supports toxicity after 40 treatments**
- i. Where do we find an effect? Is there a benefit for going past 60?
- j. Need to compromise
- k. **Permanent effect was seen at 40 treatments - Dr. Harch**
- l. **Dr. Rockswold says 40 treatments is safest**
- m. **What is the vote on maximum number of treatments?**
  - i. 80 treatments
  - ii. 60 treatments
- n. **40 treatments - All agreed**

**12. How many days a week?**

- a. Dr. Harch likes once a day, 6 days a week because it gives the brain time to adapt
- b. Staffing may not allow 6 days, may not be open on weekends
- c. What is practical?
- d. Monoplace is easy to do multiple per day but multiplace can only do one a day
- e. **Vote on how many days**
  - i. **5 days All Agreed**
  - ii. 6 days
  - iii. 7 days

**13. How many treatments per day?**

- a. What is the rationale for treatments per day?
- b. Most multiplace centers do not have the capacity to do more than once a day treatments
- c. **No real data on multi-treatment effect**
- d. **Hours separated is minimum of 3 hours - but not sorted out and studied thoroughly - Dr. Harch**
- e. **Vote on How many treatments per day**
  - i. **1 a day All Agreed**
  - ii. 2
  - iii. 3

14. What do we do with patients who miss treatments?
- a. Dr. Harch - important thing is total number of treatments and intermittent does not affect results
  - b. Dr. Rockswold - what is the tolerable gap between treatments?
  - c. Dr. Harch showed improvements in a patient who had a 5 day absence
  - d. Twelve weeks maximum study time
  - e. Vote How many days to finish protocol
    - i. 12 weeks
    - ii. 10 weeks All agreed
15. Complications Exclusions
- a. Since we've eliminated 2.5 ata, if they show one complication, patient should be eliminated
    - i. Pnuemothorax - Exclude
    - ii. O2 Seizures - Exclude
    - iii. Otic Barotrauma - Include
    - iv. Sinus Barotrauma - Include
    - v. Claustrophobia - Selection Criteria - can continue as long as not on drugs
    - vi. Myopia - Include Stay in protocol and gets monitored
16. Do we need to prepare patients for the chamber with prophylaxis?
- a. All agrees not to give them anything
17. Do we need to screen individuals with a chest x-rays prior to HBOT?
- a. Do we need screening
    - i. Chest x-rays 8 votes for, 1 opposed
    - ii. Within the last 6 months without other significant intervention
    - iii. Visual acuity All agreed
18. Do patients need to be monitored in some capacity?
- a. No monitoring - All Agreed
19. Do we need to do a Pre and Post vital signs? (Heart rate, Blood pressure, temperature, respiratory rate)
- a. None 0 vote
  - b. Just Before Every Treatments 1 votes
  - c. Before and After 12 votes
20. Do We need to do TEED on Patients
- a. Vote on TEEDs
    - i. No exams 0 votes
    - ii. Before Every exam 0 votes
    - iii. Before and after every exam 6 votes
    - iv. As needed 7 votes
  - b. We need a pre and post dive checklist - CDR Kass
21. How fast to depth
- a. All agrees as Tolerated per patient
22. Timing of Evaluations
- a. Voting on timing
    - i. Never 0 votes
    - ii. Before and as needed every treatment All Agreed
    - iii. Before and after every treatment 0 votes
    - iv. Monthly 0 votes
23. Pre and Post Checklist
- a. Vital Signs

**b. Ear complaints vs. TEED**

**24. How do we do a sham?**

- a. Take them to pressure to 1.2 ata and then bleed off for the duration of the 60 minutes and then pressurize again to 1.2 ata briefly before end of treatment
- b. For multiplace to not exceed minimum chamber pressure
- c. Monoplace has to be plumbed for both oxygen and air
- d. concern is that most monoplace chambers only pressurizes with Oxygen
- e. Sham can not be done on oxygen
- f. Voting on Sham procedure**
  - i. Do nothing with pressure
  - ii. Tweak pressure in the beginning
  - iii. Tweak pressure beginning and end

**25. Leaving Checklist and Sham for Parking lot.... Break Out concluded**