# DoD Randomized Controlled Trials on the Efficacy of $HBO_2$ for mTBI

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LTC Rob Price, MD
4th Infantry Division
HOPPS/BIMA/NORMAL Studies Site PI
Outcomes Assessment Center
Ft. Carson, Colorado

# Disclaimer

Opinions, interpretations, conclusions, and recommendations are those of the presenter and are not necessarily endorsed by the other members of the $HBO_2$ research consortium, the $4^{th}$ Infantry Division, the U.S. Army Medical Materiel Development Activity, the U.S. Army Medical Research and Materiel Command, or the Department of Defense .

# Agenda

- mTBI Background
- Literature Review
- Air Force Study – *Wolfe et al*
- Navy Study – *Cifu et al*
- HOPPS – *Miller et al*
- BIMA – *Weaver et al*

## Lethality of War Wounds among U.S. Soldiers.*

| War | No. Wounded or Killed in Action | No. Killed in Action | Lethality of War Wounds |
|---|---|---|---|
| | | | % |
| Revolutionary War, 1775–1783 | 10,623 | 4,435 | 42 |
| War of 1812, 1812–1815 | 6,765 | 2,260 | 33 |
| Mexican War, 1846–1848 | 5,885 | 1,733 | 29 |
| Civil War (Union Force), 1861–1865 | 422,295 | 140,414 | 33 |
| Spanish-American War, 1898 | 2,047 | 385 | 19 |
| World War I, 1917–1918 | 257,404 | 53,402 | 21 |
| World War II, 1941–1945 | 963,403 | 291,557 | 30 |
| Korean War, 1950–1953 | 137,025 | 33,741 | 25 |
| Vietnam War, 1961–1973 | 200,727 | 47,424 | 24 |
| Persian Gulf War, 1990–1991 | 614 | 147 | 24 |
| War in Iraq and Afghanistan, 2001–present | 10,369 | 1,004 | 10 |
| | Nov. 2nd, 2015 52,312 | 5,363 | 10 |

* Data are from the Department of Defense.[1,3]

Gawanda, Atul MD, NEMJ Dec 2004/ http://icasualties.org/oif/ - DIOR

# Survivability Improved

- Revolutionary War – 57% survived their wounds
- OEF/OIF Today – 90% survive their wounds

https://www.dmdc.osd.mil/dcas/pages/report_sum_reason.xhtml

# Body Armor Changes Injury Patterns and Survivability

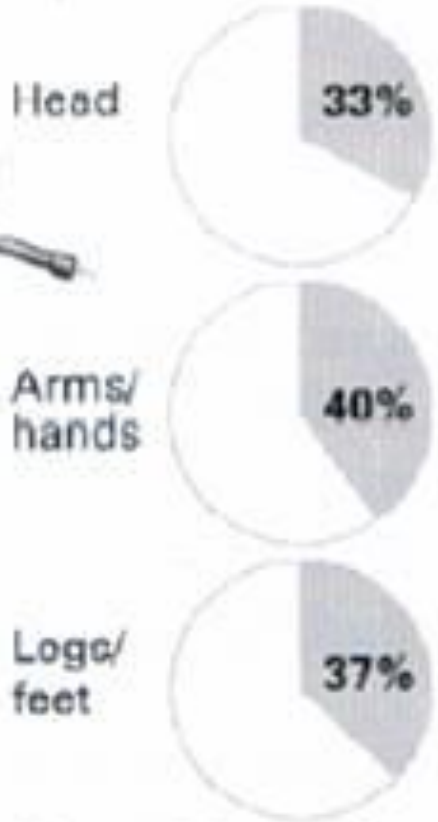
## Armor

**Kevlar helmet**
Up to 40 percent more resistant to penetration than steel helmets.

**Interceptor vest**
Outer Kevlar vest and inch-thick ceramic inserts. Removable throat and groin protectors.

**Vulnerable**
Limbs, sides, and neck.

## Where Injured




*Most soldiers receive multiple injuries; totals add to more than 100 percent.*

# Mine Resistant Ambush Protected (MRAP)

# Traumatic Brain Injury (TBI)

- "Signature Injury" of the Global War on Terrorism (GWOT) or Overseas Contingency Operations (OCO)

- Incidence:  320,000 with deployment related TBI – US 1.4 million

# What is a traumatic brain injury?

A traumatic brain injury (TBI) is a blow or jolt to the head or a penetrating head injury that disrupts the function of the brain. Not all blows or jolts to the head result in a TBI. The severity of such an injury may range from "mild," i.e., a brief change in mental status or consciousness to "severe," i.e., an extended period of unconsciousness or amnesia after the injury. A TBI can result in short or long-term problems with independent function.

# Classification of TBI

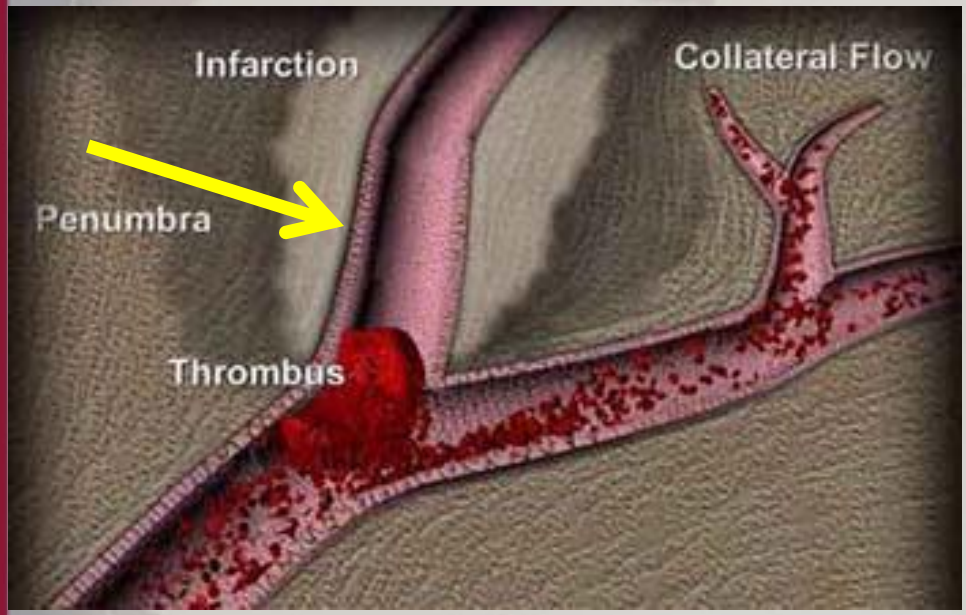
| Criteria | Mild | Moderate | Severe |
|---|---|---|---|
| Structural imaging | Normal | Normal or abnormal | Normal or abnormal |
| Loss of Consciousness (LOC) | 0–30 min | > 30 min and < 24 hrs | > 24 hrs |
| Alteration of consciousness/mental state (AOC) * | a moment up to 24 hrs | > 24 hours. Severity based on other criteria | |
| Post-traumatic amnesia (PTA) | 0–1 day | > 1 and < 7 days | > 7 days |
| Glascow Coma Scale (best available score in first 24 hours) | 13-15 | 9-12 | < 9 |

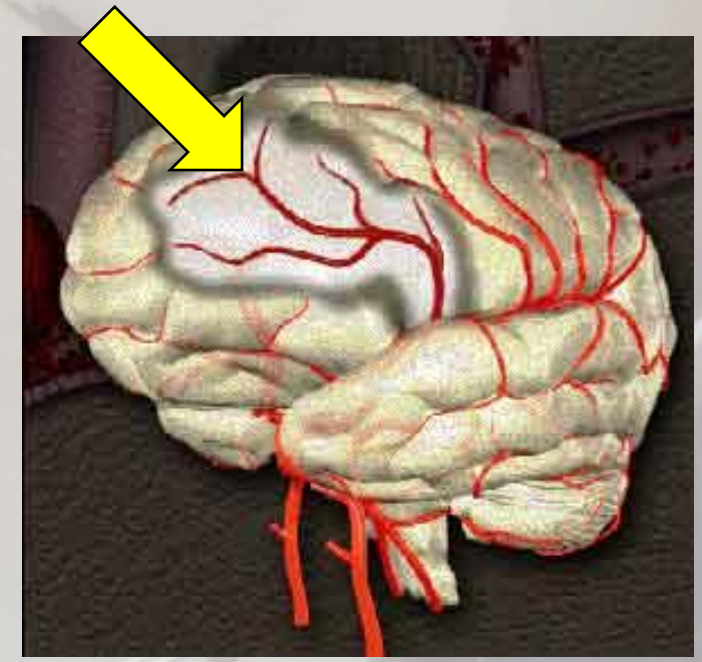
* Alteration of mental status must be immediately related to the trauma to the head. Typical symptoms would be: looking and feeling dazed and uncertain of what is happening, confusion, difficulty thinking clearly or responding appropriately to mental status questions, and being unable to describe events immediately before or after the trauma event.

VA/DoD Clinical Practice Guideline
http://www.healthquality.va.gov/management_of_concussion_mtbi.asp

# $HBO_2$ and Ischemic Penumbra

Brain ischemic penumbra – center region of brain death, surrounded by dysfunctional, but potentially viable tissue (penumbra), surrounded by normal tissue.



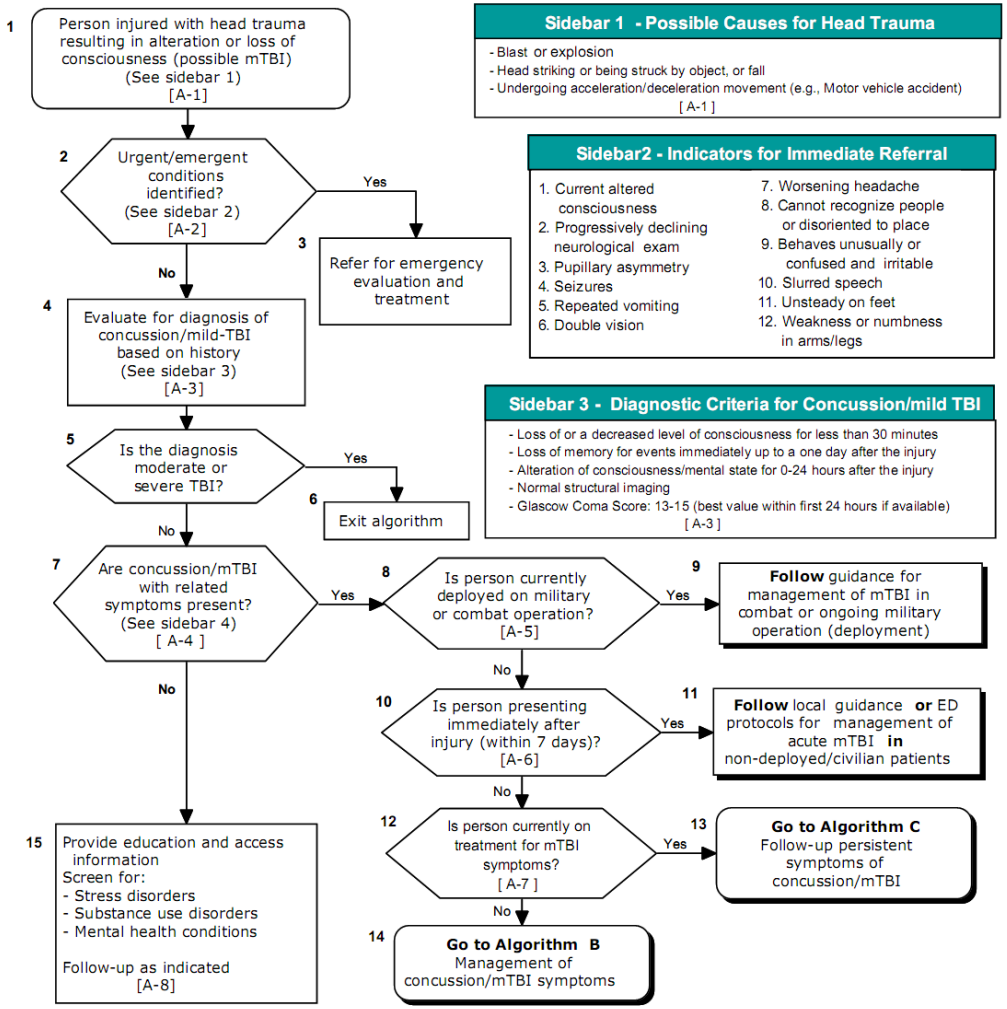



Therapy might favorably influence the ischemic penumbra.

# WHEN TO TREAT

- Symptoms of mild TBI or concussion may resolve within hours to days or may improve over 1 – 3 months. However if symptoms persist and do not improve, medical treatment should be sought.
- All service members involved in a blast are seen to eliminate stigma.
- Risk of persistent symptoms increased with recurrent concussions.

# VA/DoD Clinical Practice Guideline for Management of Concussion/mild-Traumatic Brain Injury
## A: Initial Presentation




### Sidebar 1 - Possible Causes for Head Trauma

- Blast or explosion
- Head striking or being struck by object, or fall
- Undergoing acceleration/deceleration movement (e.g., Motor vehicle accident)

[ A-1 ]

### Sidebar2 - Indicators for Immediate Referral

1. Current altered consciousness
2. Progressively declining neurological exam
3. Pupillary asymmetry
4. Seizures
5. Repeated vomiting
6. Double vision
7. Worsening headache
8. Cannot recognize people or disoriented to place
9. Behaves unusually or confused and irritable
10. Slurred speech
11. Unsteady on feet
12. Weakness or numbness in arms/legs

### Sidebar 3 - Diagnostic Criteria for Concussion/mild TBI

- Loss of or a decreased level of consciousness for less than 30 minutes
- Loss of memory for events immediately up to a one day after the injury
- Alteration of consciousness/mental state for 0-24 hours after the injury
- Normal structural imaging
- Glascow Coma Score: 13-15 (best value within first 24 hours if available)

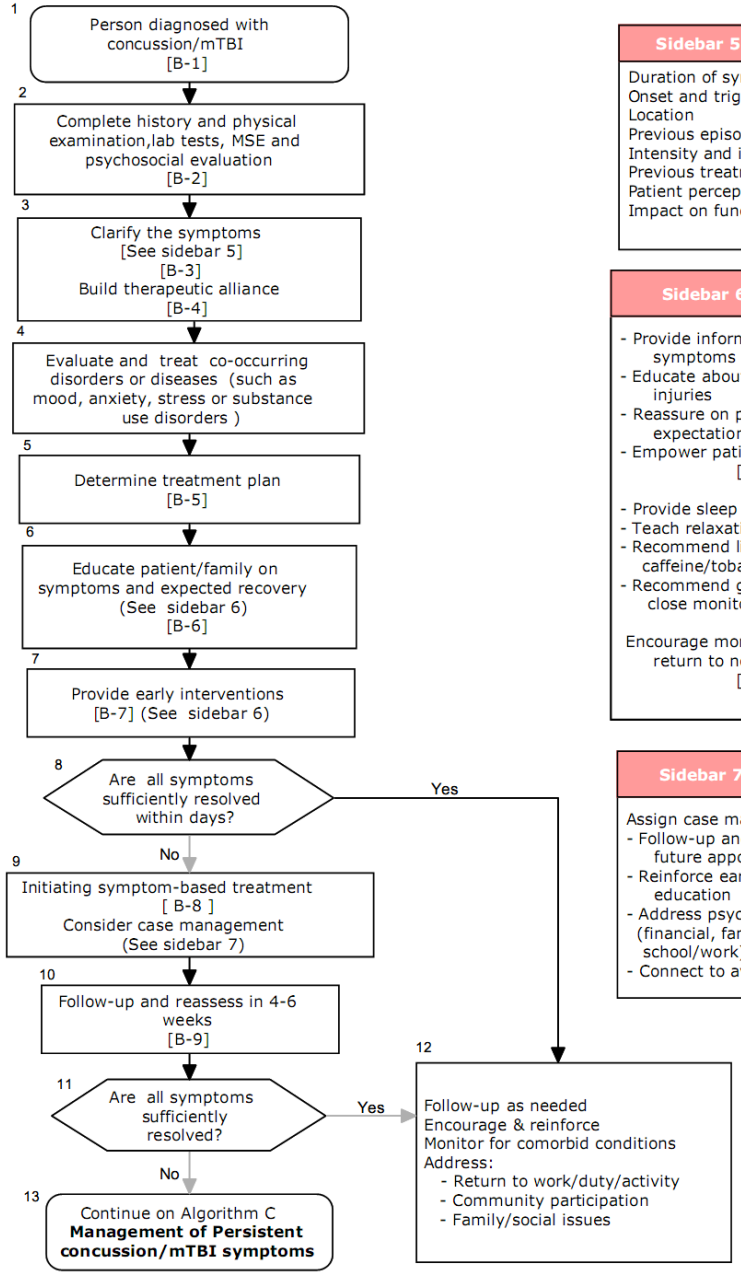
[ A-3 ]

### Sidebar 4 - Post-Concussion/mTBI Related Symptoms *

| Physical Symptoms : | Cognitive Symptoms : | Behavior/Emotional Symptoms : |
|---|---|---|
| Headache, dizziness, balance disorders, nausea, fatigue, sleep disturbance, blurred vision, sensitivity to light, hearing difficulties/loss, sensitivity to noise, seizure, transient neurological abnormalities, numbness tingling | Attention, concentration, memory, speed of processing, judgment, executive control. | Depression, anxiety, agitation, irritability, impulsivity, aggression. |

* Symptoms that develop within 30 days post injury

# VA/DoD Clinical Practice Guideline for Management of Concussion/mild-Traumatic Brain Injury
## B: Management of Symptoms




### Sidebar 5: Symptom Attributes

Duration of symptom
Onset and triggers
Location
Previous episodes
Intensity and impact
Previous treatment and response
Patient perception of symptom
Impact on functioning
[ B-3 ]

### Sidebar 6: Early Intervention

- Provide information and education on symptoms and recovery
- Educate about prevention of further injuries
- Reassure on positive recovery expectation
- Empower patient for self management

[ B-6 ]

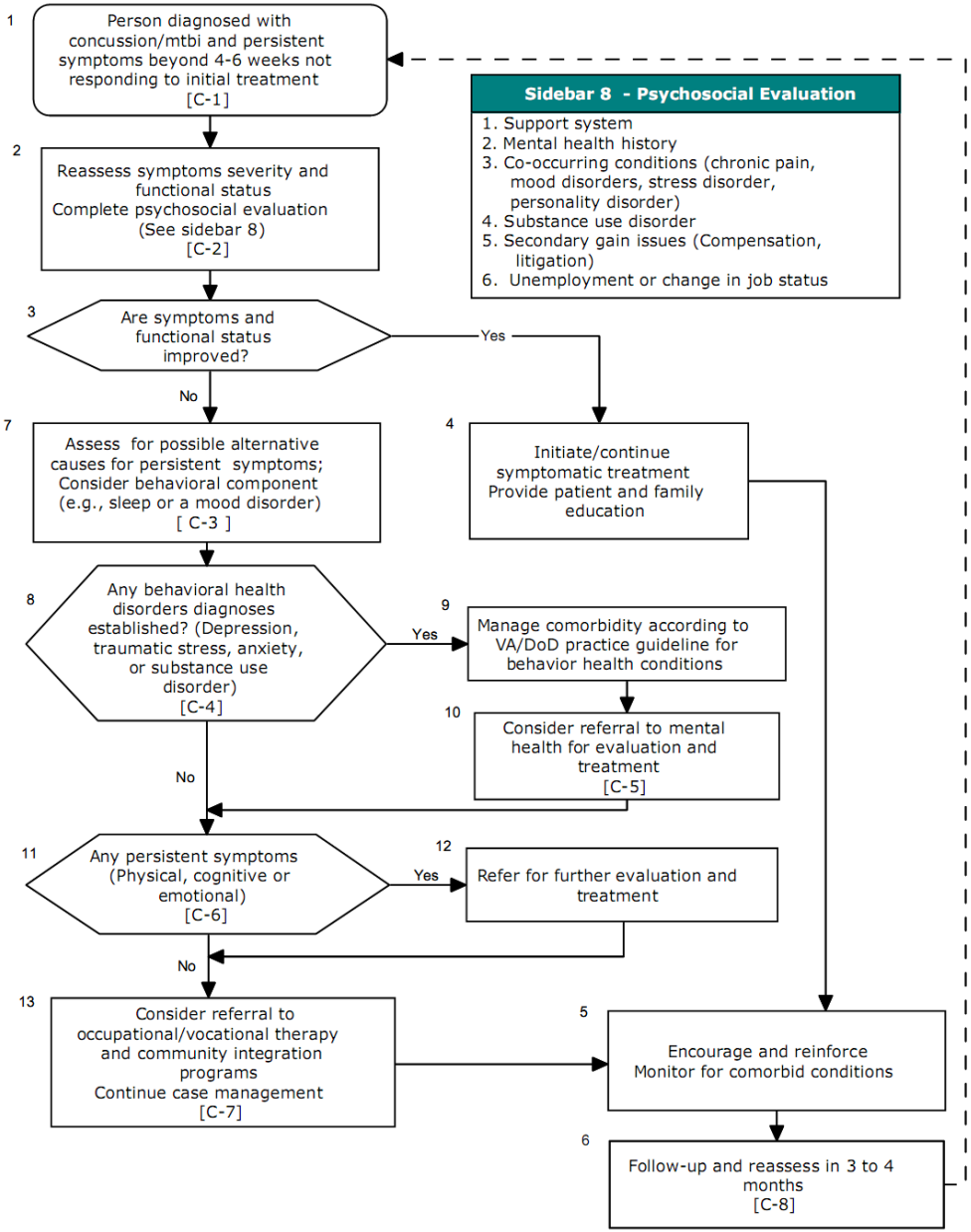
- Provide sleep hygiene education
- Teach relaxation techniques
- Recommend limiting use of caffeine/tobacco/alcohol
- Recommend graded exercise with close monitoring

Encourage monitored progressive return to normal duty/work/activity
[ B-7 ]

### Sidebar 7: Case Management

Assign case manager to:
- Follow-up and coordinate (remind) future appointments
- Reinforce early interventions and education
- Address psychosocial issues (financial, family, housing or school/work)
- Connect to available resources

# VA/DoD Clinical Practice Guideline for Management of Concussion/mild-Traumatic Brain Injury
## C: Follow-up Persistent Symptoms



# No definitive treatment

- Testimonials
  - Harch Hyperbarics - http://www.hbot.com/
  - Healing Heroes Network - http://healingheroes.org/
  - Rocky Mountain Hyperbaric Institute – http://rockymountainhbot.com/
  - Pikes Peak Hyperbarics – http://www.pikespeakhyperbaric.com/sos-program/sos-overview
- Lobbyist and patient advocacy groups
- Political pressure on DoD to provide this possible definitive treatment for ALL wounded Warriors with TBI

# Consensus Conference

**Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury and**

**Defense and Veterans Brain Injury Center**

**Consensus Conference on**

**Cognitive Rehabilitation for Mild Traumatic Brain Injury**

**27 and 28 April 2009, Washington, DC**

- H.R. 4568: TBI Treatment Act
  - Rep. Peter Sessions (R-TX)
  - Appropriate funds to empirically treat all service members and veterans with TBI

# Senator Mark Allen

Serving Senate District 4: LeFlore and Sequoyah Counties

search site



## Blog



### Oklahoma Takes the Lead in Recognizing TBI Treatments for Veterans

07 May 2014
0 Comments
in 2014 Session Update, Legislation, Veterans
by Mark Allen

SB 1604, The Oklahoma Veterans Traumatic Brain Injury Treatment and Recovery Act of 2014, authored by Senator Mark Allen and Representative John Bennett, was signed into law yesterday by Governor Mary Fallin. The bill goes into effect November 1, 2014.

The first of its kind in the country, the bill states that any Oklahoma veteran who has been diagnosed with a traumatic brain injury (TBI) and prescribed hyperbaric oxygen treatment (HBOT) by an authorized medical professional may receive HBOT at any facility in the state that has a hyperbaric chamber.

Hyperbaric chambers offer oxygen at a level higher than atmospheric pressure. Studies show the 100 percent oxygen chambers trigger the brain's neurons and harness the healing power of oxygen.

Subject to the availability of funding, the treatment will be paid for with private dollars at no cost to the

## Contact

OKLAHOMA STATE CAPITOL
Senator Mark Allen
2300 N. Lincoln Blvd., Rm 415
Oklahoma City, OK 73105

# Two Approaches

- The population at risk for TBI was not co-located where the DoD had hyperbaric medicine

– Take Service Members to the chambers…

– Take chambers to the Service Members…

# Challenges to studying the efficacy $HBO_2$ for mTBI

- Frequent lack of pre-injury baseline data
- Complicated by polypharmacy
- Significant time commitment (8 + weeks)
- Post-traumatic stress disorder (PTSD) is a common co-morbid condition
- Refractory patients hesitant to get placebo or “sham” arm of an RCT

# $HBO_2$ for Acute TBI

- 1967: K.H. Holbach (Germany), begins treating severe, acute TBI and CVA
  - 2-3 atm abs, 30-60 minutes
  - Saw improvement in EEG, biochemical markers, rCBF
- 1976: Artru, Chacornac, Deleuze (France); RCT, 60 patients
  - 2.5 atm abs, 60 minutes, daily for 10 days, 4 days off, repeated until patient died or regained consciousness
  - No difference in mortality at 12 months
  - Trends toward improvement in duration of coma with $HBO_2$, but not statistically significant
- 1983-94: Rockswold, Ford, et al.; RCT in acute, severe TBI
  - 1.5 atm abs, every 8 hours, until subject awake or brain dead
  - $HBO_2$ improved mortality
  - Worse functional outcome in $HBO_2$ group
- 2001: Rockswold, et al. $HBO_2$ on physiological measures, no control group
  - 1.5 atm abs daily for 6 days
  - Improvements in cerebral blood fall and intracranial pressure
- 2009: Rockswold, et al; RCT
  - $HBO_2$ improved biochemical markers

# History of HBO2 at 1.5 atm abs for brain injury

- 1973: Holbach and Caroli, Bonn, Germany
  - From 1967 to 1973, over 700 HBO2 sessions for acute brain injury (stroke & TBI),
  - Examined cerebral glucose metabolism and acid/base balance of the brain in 102 patients that received 267 courses of HBO2
    - Discovered that 1.5 atm abs was optimal, 2.0 atm abs was adverse
- 1976: Holbach, Wassman, and Hoheluchter
  - Used 1.5 atm abs for chronic stroke
- 1980: Neubauer and End, Florida
  - Used 1.5 atm abs for chronic stroke, 2.0 atm abs for acute stroke
  - Subsequently used 1.5 atm abs for other types of chronic brain injury
- 1994: Harch abstract
  - SPECT brain imaging and “low pressure HBOT” for treatment of chronic brain injury (including TBI)

# History of HBO2 at 1.5 atm abs for brain injury

- 2004: Barrett et al. UHM; 31:395-406
  - Single-center prospective, non-randomized study
  - 5 subjects 3 years post-brain injury 120 HBO2 exposures at 1.5 atm abs
  - No significant objective changes
- 2006: Shi et al. Chin Med J 2006; 119: 1978-82.
  - 252 with symptomatic brain injury with positive SPECT at least 1 mos post injury
  - 20 HBO2 exposures at 0.1 Mpa with 96% oxygen
  - 160 subjects with “normal” SPECT, 92 of persistent abnormals had improved blood flow
- 2007: Harch et al. Brain Res;1174:120-9.
  - Rat model of chronic traumatic brain injury.
  - Control, sham, HBO2 at 1.5 atm abs x 90 min BID for 80 sessions
  - Improvement in spatial learning and increased vascular density in the hippocampus

# Open Label Data from Non-Randomized Case Series at 1.5 mTBI

- 2011: Harch et al. J. of Neurotrauma; 28:1– 18
  - 16 Veterans 1-4 years post TBI with chronic symptoms
  - exposed to $HBO_2$ 1.5 ATA x 40 days with twice daily dive sessions
  - ~ 10 % improvement in memory and neuropsych tests
  - Up to 51% improvement in self-reported anxiety and depression scores
  - Self-reported 'improved to normal' cognition (50→ 67%) , emotional (32→61%); physical (47→66%)
  - Brain SPECT scans showed improved metabolism after HBO2
  - Assessment immediately post rx; No data on durability of response
  - Design does not allow assessment of contribution of $HBO_2$, and results are in range of placebo/ Hawthorne effect

# UHMS and HBO for mTBI

- Position Statement

Currently available scientific literature does not support an endorsement of $HBO_2$ for chronic brain injury and recommended prospective, randomized, and controlled clinical trials to assess whether $HBO_2$ therapy is associated with favorable risk-benefit and cost-benefit ratios for TBI.

# Agency for Healthcare Research and Quality (AHRQ)

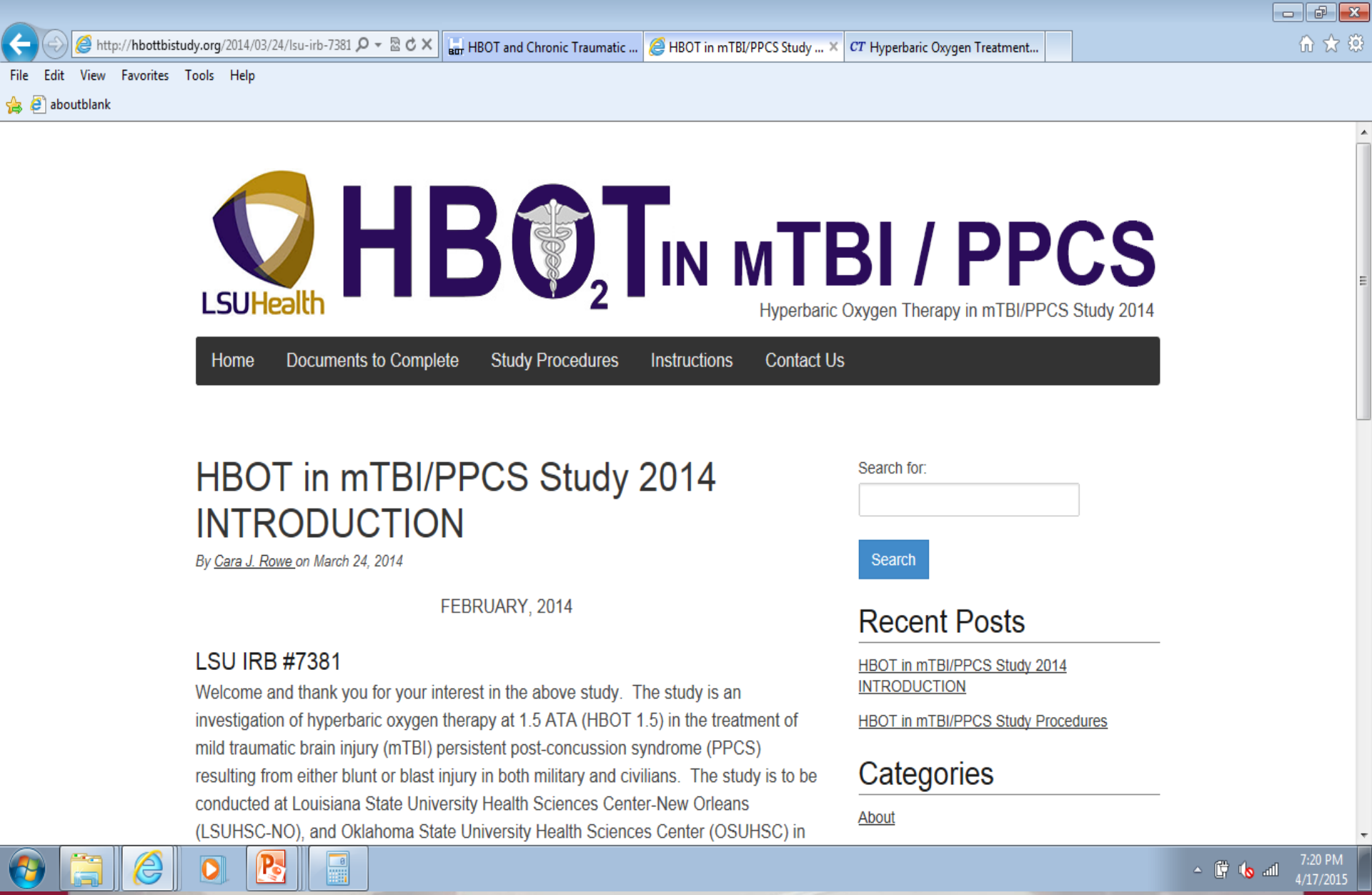
"Although they are cited frequently, the case series and time-series studies of $HBO_2$ for TBI patients had serious flaws. There were no high-quality studies of the use of $HBO_2$ to improve function and quality of life in patients with chronic, stable disabilities from TBI. The most important gap in the evidence is a lack of a good quality time-series study or controlled trial of the effects of $HBO_2$ on cognition, memory, and functional status in patients with deficits due to mild and moderate chronic TBI."

# Department of Health and Human Services (DHHS)

"The US Department of Health and Human Services Centers for Medicare and Medicaid Services (CMS) limits reimbursement for HBO2 therapy to that which is administered in a chamber for the indications listed in Table 1. CMS does not authorize HBO2 as standard of care for TBI, nor is it a reimbursable benefit for civilian providers by third party payers. "

# The Cochrane Collaboration
# Cochrane Reviews

"The routine application of HBOT to these patients cannot be justified from this review. Given the modest number of patients, methodological shortcomings of included trials and poor reporting, the result should be interpreted cautiously. An appropriately powered trial of high methodological rigour is required to define which patients, if any, can be expected to benefit most from HBOT."




https://www.clinicaltrials.gov/ct2/show/NCT02089594?term=HBOT+MTBi+PPCS&rank=1

# $HBO_2$ for chronic impairments due to TBI, RCT

- *2013: Boussi-Gross, et al.*
  - N=90; PCS from mild TBI; 1 to 6 yrs post-injury
  - Randomized to HBO2 v Control (no sham), then the Controls exposed to HBO2 two months later
  - HBO2 – 1.5 ATA x 60 (90) min x 40 sessions
  - Significant improvement in **ALL** cognitive measures and Quality of Life ($p<0.005$).
  - Brain SPECT showed improved brain metabolism after HBO2

# The Effect of Hyperbaric Oxygen on Symptoms Following Mild Traumatic Brain Injury

*2012: Wolf G. et al; J Neurotrauma*

# U.S. Air Force School of Aerospace Medicine (USAFSAM)

- Blinded RCT of 50 Service Members with post concussive symptoms after 1 or more concussions: 1.3 air vs. 2.38 atm abs HBO2
- Outcome measures before and after 30 daily sessions; and 6 weeks later
  - Computer neurocognitive tests: ImPACT, Braincheckers –ANAM, TOVA
  - Symptoms: ImPACT and PCL-M
- Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) and Post-traumatic Disorder Checklist-Military (PCL-M), ImPact total score - **no difference with HBO2, but both groups improved more than expected.**
- Why did the sham group improve?
  - Placebo effect, Hawthorne Effect
  - Daily interactions with staff
  - Physiological effects of increased partial pressures of N2 and O2

# The Effect of Hyperbaric Oxygen on Persistent Postconcussion Symptoms

*2013: Cifu D. et al; J Head Trauma*

*Courtesy*, Capt. Hart, Dr. Cifu

# Navy-VCU-NOMI: Participants/Intervention

- Active duty, hx mTBI 4 months to 2 years prior, still having post concussive symptoms
- 60 subjects randomly assigned to 1 of 3 chamber groups (all subjects pressurized to 2.0 atm abs)
  - #20 - 2.0 atm abs oxygen equivalent (100% O2 / 0% N2)
  - #20 - 1.5 atm abs oxygen equivalent (75% O2 / 25% N2)
  - #20 - 1.0 atm abs air equivalent (10.5% O2 / 89.5% N2)
- 12 subjects tested/began chamber sessions every 2.5 months
- 40 sessions per subject (8 weeks), 1 chamber exposure/day

LTC Rob Price/ 719-503-7506/rob.price@us.army.mil

128 Screened for Eligibility

59 Excluded
- 30 Refused to Participate
- 29 Failed to Meet Inclusion Criteria

61 Randomized

| | | |
|---|---|---|
| 21 Randomized to Sham Condition<br>21 Received Intervention as Assigned | 21 Randomized to 1.5 ATA Condition<br>21 Received Intervention as Assigned | 19 Randomized to 2.0 ATA Condition<br>19 Received Intervention as Assigned |
| 21 Assessed at 2-week Follow-Up | 21 Assessed at 2-week Follow-Up | 18 Assessed at 2-week Follow-Up<br>1 Lost to Follow-up; Unavailable |
| 20 Assessed at 12-week Follow-Up<br>1 Lost to Follow-Up; Not located | 20 Assessed at 12-week Follow-Up<br>1 Lost to Follow-Up; Declined Participation | 19 Assessed at 12-week Follow-Up |
| 21 Included in This Analysis | 21 Included in This Analysis | 19 Included in This Analysis |

# Navy-VCU-NOMI: Participants/Intervention

- Assessment Schedule:
  - Baseline
  - After completion of chamber sessions (2 month)
  - 3 months later (5 months post-enrollment)
- Assessment battery requires 5 hours:
  - Symptom Questionnaires
  - Structured interviews
  - Neuropsychological
  - Neurophysiological (Eye Tracker, Balance)
- **No difference in symptoms by allocation, but apparent improvement in many**

*Courtesy*, CAPT Hart, Dr. Cifu

# Results

- ***No differences between any of the groups*** on any aspect of the **primary** outcome measure (RPQ), including subscales RPQ-3 and RPQ-13
  - Within group comparisons (pre/post intervention) were not significant
- ***No differences between any of the groups*** on the total score of the **secondary** measure (PCL-M)
  - Within group differences showed improvement (pre/post):
    - Sham: 6.7 point improvement
    - $HBO_2$ 1.5 ATA: 6.2 point improvement
    - $HBO_2$ 2.0 ATA: 13.9 point improvement (statistically improved)

One-way ANOVA conducted on total RPQ score, subscales RPQ-3 and RPQ-13, and all individual items

One-way ANOVA conducted on total PCL-M score

*Courtesy*, CAPT Hart, Dr. Cifu

# Results

RPQ Sub-analysis: Within group differences on individual symptoms

- Sham group (air equivalent) showed no significant differences between pre/post compression scores
- 1.5 ATA equivalent group showed a significant increase (worsening) in light sensitivity
- 2.0 ATA equivalent group showed a significant decrease (improvement) on noise sensitivity and frustration/ impatience
- No trends in $HBO_2$ dose indentified

*Courtesy*, CAPT Hart, Dr. Cifu

# Results

PCL-M Sub-analysis: Within group differences on individual symptoms

- Sham group showed significant improvement on super alertness/watchfulness and being easily startled between pre-post compression scores
- 1.5 ATA equivalent group showed a significant improvement on super alertness/watchfulness
- 2.0 ATA equivalent group showed a significant improvement on being upset when reminded of a stressful event, super alertness/watchfulness and total score

*Courtesy*, CAPT Hart, Dr. Cifu

# Conclusions

- Study duplicated $HBO_2$ doses most often used clinically and recommended by advocates
- No main-effect treatment differences in post-concussion symptoms were found between sham compression, 1.5 ATA, or 2.0 ATA groups
  - Suggests anecdotal benefits are neither due to increased partial pressures of nitrogen or oxygen
- 2.0 ATA group showed only within group statistical improvement on total PCL-M
- 3 Month follow-up results are in analysis

*Courtesy*, CAPT Hart, Dr. Cifu

# Effects of Hyperbaric Oxygen on Symptoms and Quality of Life Among Service Members With Persistent Postconcussion Symptoms (HOPPS)

*2014: Miller S. et al; JAMA Internal Medicine*

*Courtesy*, COL Scott Miller

# Outcome Measures

- **PCS has a neurologic and psychiatric component, and outcome measures are not validated**
- **Primary:** Rivermead Post Concussion Symptom Questionnaire
- **Secondary:** Neurobehavioral Symptom Inventory
  - PTSD Symptoms: PCL–C (self-report questionnaire)
  - Sleep, pain, depression and anxiety symptoms
  - HRQoL measures – Satisfaction with Life Survey
    Short Form 36 Health Survey
  - Test of memory malingering (effort)
  - Neurologic: Sharpened Romberg; Smell testing
  - Psychomotor: Grooved Pegboard
  - ANAM (automated cognitive function battery)
  - Cognitive Test Battery
    - Stroop
    - TMT
    - D-KEFS
    - CVLT-II
    - BVMT-R
    - WTAR

# Randomized Intervention: 1.5 ATA $HBO_2$ vs. Sham vs. Routine TBI Care

- **Three arm, randomized control trial**:

  1) Comparator: Routine TBI care (as defined by local MTF)

  2&3) Interventional Arms: Routine TBI care supplemented by a hyperbaric chamber procedure
  - Active: 1.5 ATA 100% $O_2$ for 60 min X 40 daily sessions within 10 weeks
    - Achieves plasma oxygen concentrations ~10x normal
  - Sham: 1.2 ATA room air, for 60 min X 40 daily sessions within 10 weeks
    - Oxygen equivalent (~2 L/min via NC)
- **Allocation : 1:1:1 stratified by study site**
- **Masking: elaborate SOP to hide gas and pressure used; blind maintained**
- **Blinding: volunteers, medical team and assessors all blinded to assignment**

# Results: Demographics

## 1.5 ATA $HBO_2$ vs. Sham vs. Routine TBI Care

286 Calls to recruiting center

96 Not eligible/ interested

140 Referred to sites for consent

37 Not eligible
29 Screening incomplete
2 Commander did not support

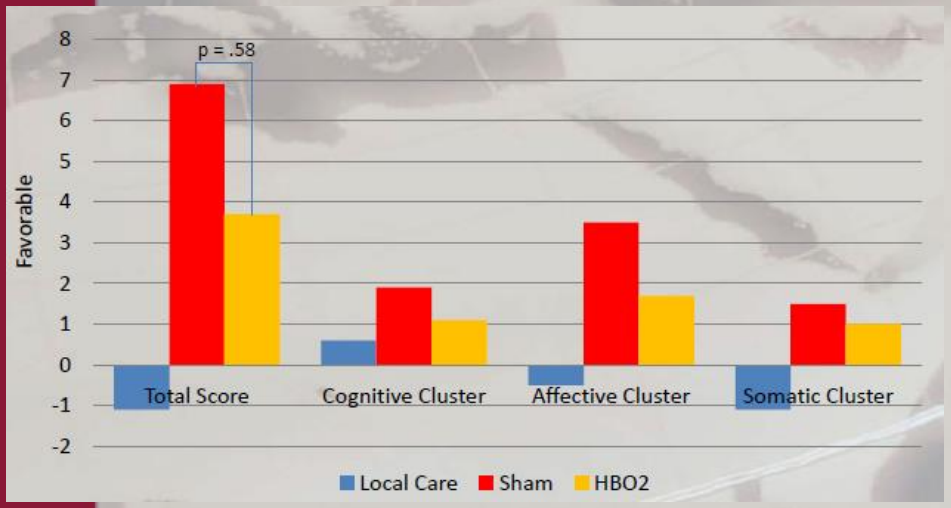
72 Enrolled

| | Local Care (n=23) | Sham (n=25) | $HBO_2$ 1.5 (n=24) |
|---|---|---|---|
| Age, mean | 30.3 | 31.4 | 32.5 |
| Sex (% male) | 96% | 96% | 96% |
| Enlisted | 91% | 96% | 96% |
| Completed some college | 65% | 72% | 63% |
| # TBIs, lifetime | 2.8 | 3.7 | 2.8 |
| Months since recent mTBI | 17.2 | 26.3 | 24.9 |
| Baseline NSI score | 33.6 | 32.6 | 34.3 |
| % PTSD (SCID) | 74% | 64% | 54% |
| Baseline PCL-C score | 51.8 | 53.5 | 48.5 |
| TOMM Retention $\geq$45 | 87% | 96% | 92% |

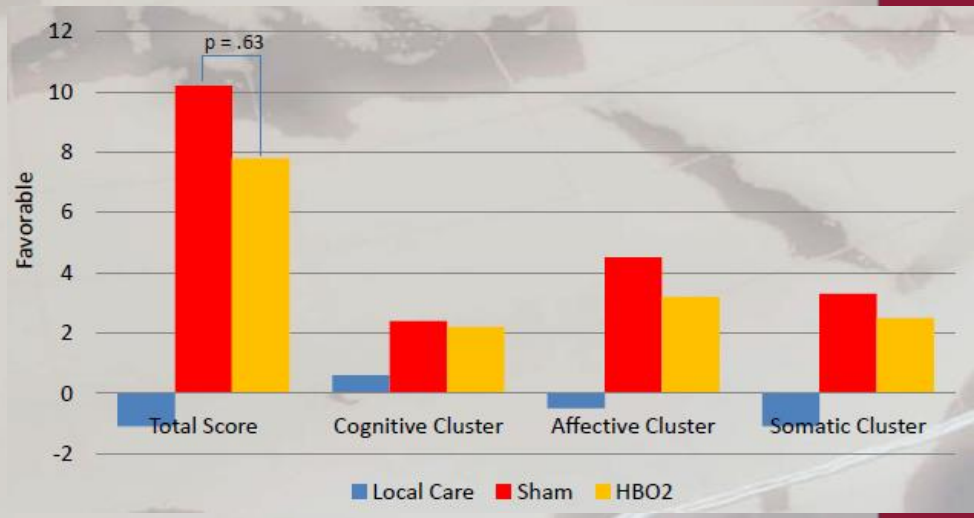
LTC Rob Price/ 719-5

# Concussion Symptoms
## Neurobehavioral Symptom Inventory (NSI)

Improvement from Baseline – Intention to Treat




Improvement from Baseline – Per Protocol

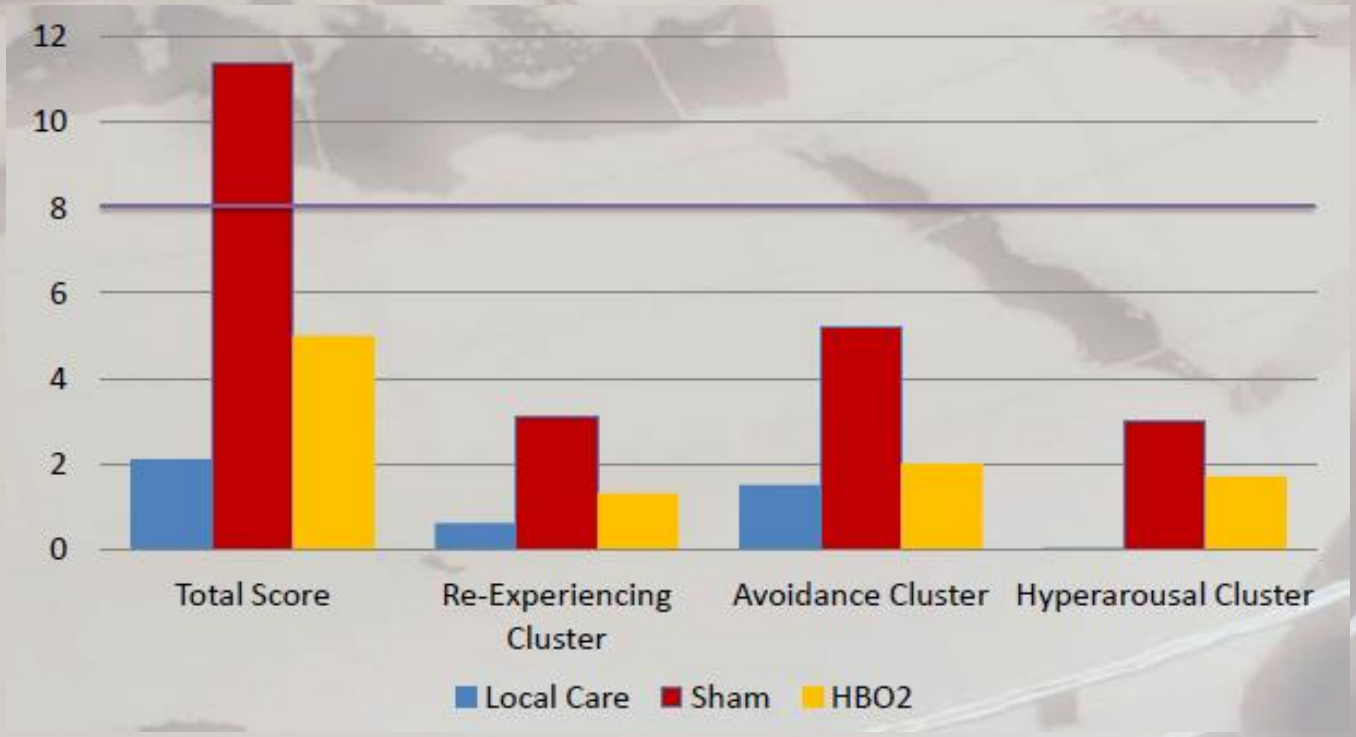



- No differences in immediate symptom responses between $HBO_2$ and sham
- Both were statistically superior to local TBI care arm, and showed maximal improvement when all 40 sessions were completed

# PTSD Symptoms

## PTSD Checklist- Civilian

### Improvement from Baseline – ITT




- By per protocol analysis, there were no differences between $HBO_2$ and sham with reductions of 9.5 and 12.8 points, respectively

- **Clinically Meaningful Change (≥ 8):** 20% local care, 35% $HBO_2$ and 52% sham

# Exploratory Analysis

## Subgroup with Baseline PTSD Scores ≥ 50

- Proponents have claimed $HBO_2$ may actually be treating PTSD, although no rational basis for a mechanism of action exists

- In this study, 39 volunteers had PCL-C scores at baseline suggestive of active PTSD
  - 84% of these carried a current DSM-4 diagnosis of PTSD
  - Responder defined as improvement of 20 points

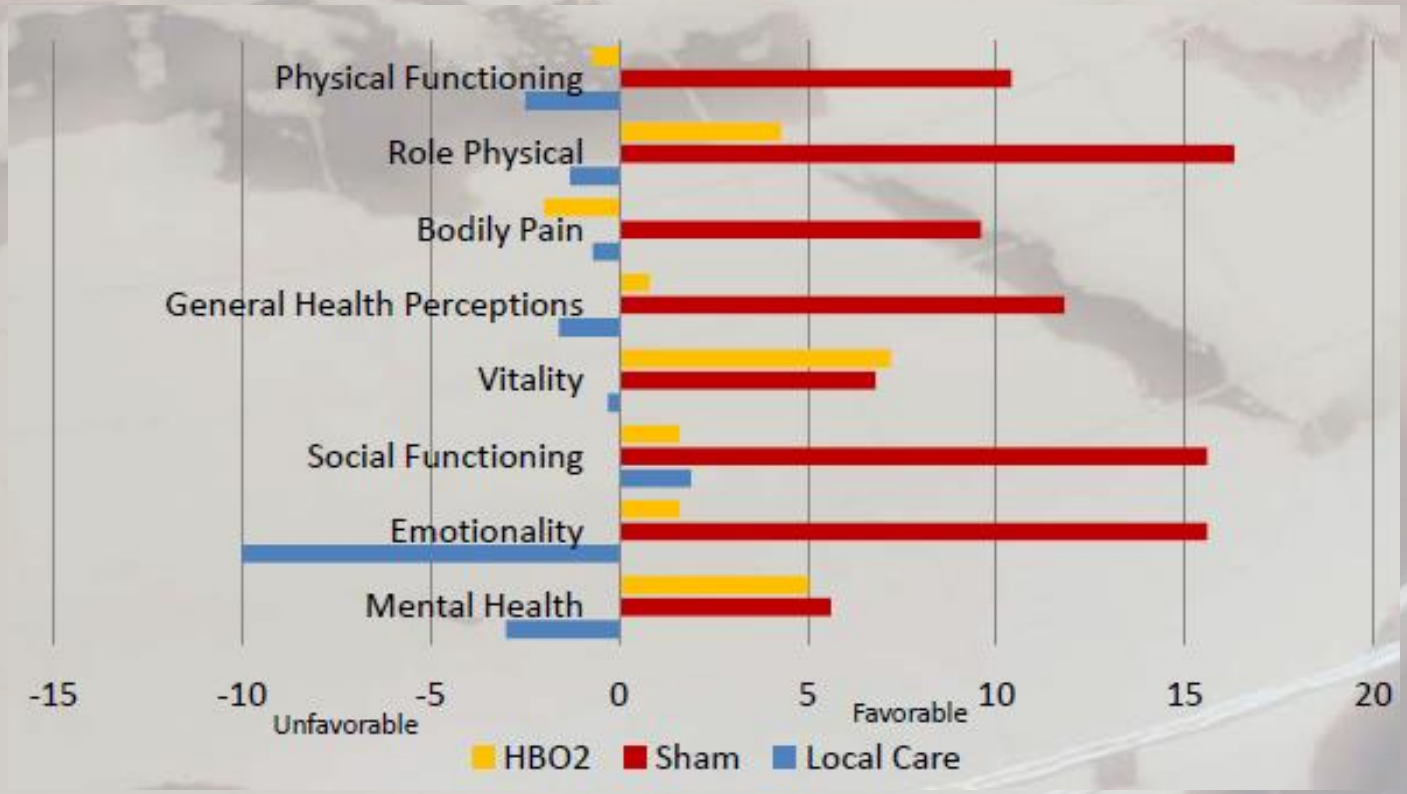
| | Local care (n=13) | HBO2 (n=13) | Sham (n=13) |
|---|---|---|---|
| Responder | 23% | 31% | 54% |
| Non-responder | 54% | 62% | 39% |

- p value ($HBO_2$ vs. sham): 0.41

# Health Related Quality of Life

## Short Form 36 Health Survey

## Change from Baseline – Health Concepts (ITT)




- Also no difference between $HBO_2$ and sham on Satisfaction with Life Scale with both showing modest improvement

# HOPPS Summary

• In this study, standard local care offered no symptomatic improvement during the 3 month observation period

• Randomization to the chamber (either sham or $HBO_2$) offered statistical and in some measures clinically significant improvement over local routine TBI care

- ➢ This could explain the anecdotal findings reported

• ***Hyperbaric oxygen at 1.5 ATA for 40 sessions offered no statistical benefit over sham in immediate relief of PCS symptoms, PTSD symptoms, or improved quality of life***

• Most likely represents placebo response to the intensive procedure

# Brain Injury and Mechanisms of Action of $HBO_2$ for Persistent Post-Concussive Symptoms after Mild Traumatic Brain Injury (BIMA)

LTC Rob Price/ 719-503-7506/rob.price@us.army.mil 

# BIMA Research Study

- Study Director: Dr. Lin Weaver, Hyperbaric SME, LDS Hospital, Salt Lake City, UT
- Objectives: Validate quality of life and symptom measures, provide longitudinal assessment of brain function and anatomy before and after HBO2
- Protocol Design: Multi-center, double blinded, randomized control trial of proposed outcome measures in chronic mTBI (60 subjects)
  - Enrollment Sites: Cohort with chronic mTBI (SOC + sham x 40 sessions)
  - Cohort with chronic mTBI (SOC + 1.5 ATA O2 x 40 sessions)
- Closed for enrollment: 31 MAY 2014
  - Ft. Carson, CO/Evans Army Community Hospital
  - Joint Base Lewis-McChord, WA/Madigan Army Medical Center
  - Camp Lejeune, NC

# BIMA Outcomes

- Measured at baseline, after 40 exposures, and at 6 months
- Most extensive outcomes for mTBI in the DoD
  - **Neuropsychiatric** – HOPPS + WHOQOL, WAIS, COWAT
  - **Neurophysiologic** – Rotary chair, VNG, stem cells, fundoscopy, computerized posturography, stem cells, EEG, dynamometer, physical exam with a neurologist, neuro-audiology, eye tracking and stem cell testing
  - **Neuroimaging** – CT angio and functional diffusion tensor MRI
- Also conducting a normative trial on “non-TBI” brains to validate outcomes – Began enrolling OCT 2013

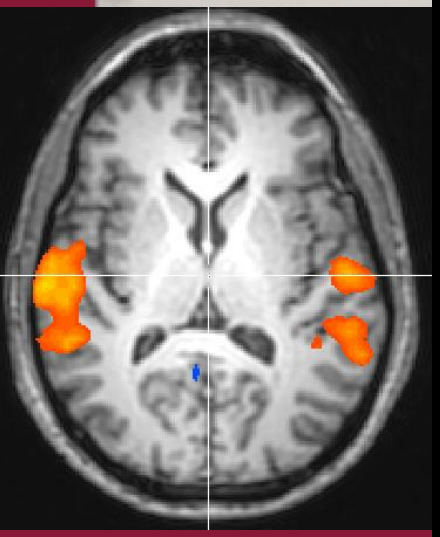
# BIMA

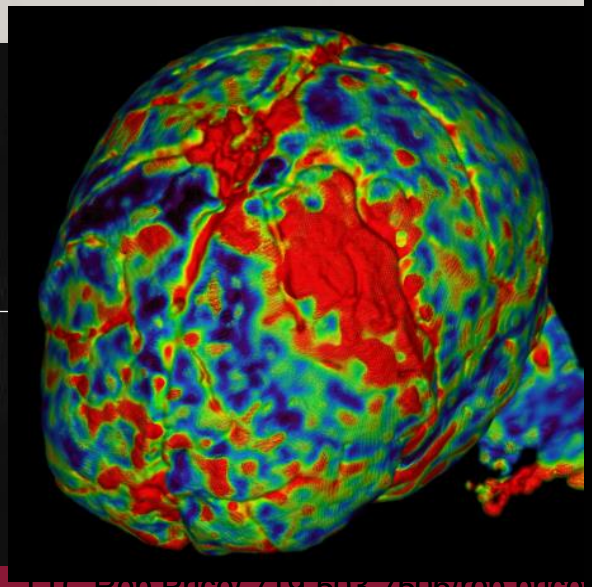
- Obtained FDA Investigational New Drug (IND) status
- Program Sponsor: MRMC
  - Enrollment complete, n = 71
- Ft. Carson, Colorado - Mobile multiplace hyperbaric chambers and research trailers.

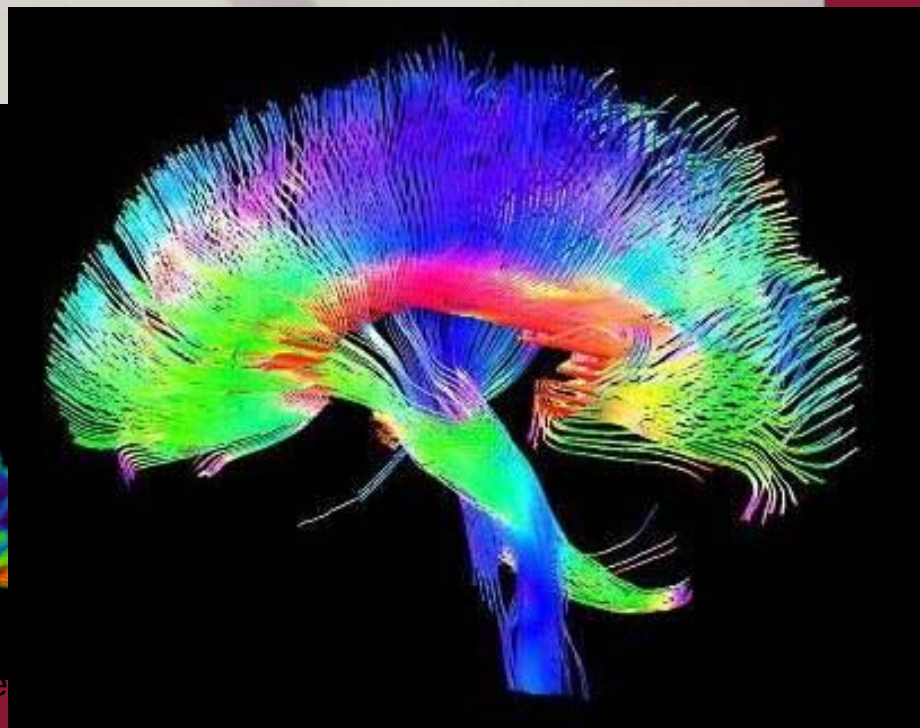
# BIMA

Evans Army Hospital, Ft. Carson, Colorado

- CT for perfusion angiography, 320 detector: whole brain perfusion, 40 seconds, 5.7 mSv
- MRI, 3 Tesla, 32 channel coil, Functional MR equipment: anatomic MRI protocol, DTI, MR Spectroscopy, fMRI (auditory, looming)



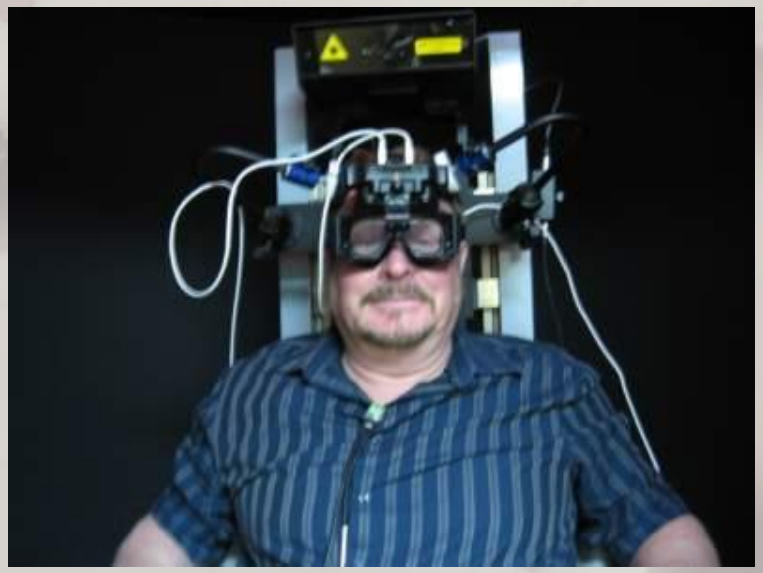


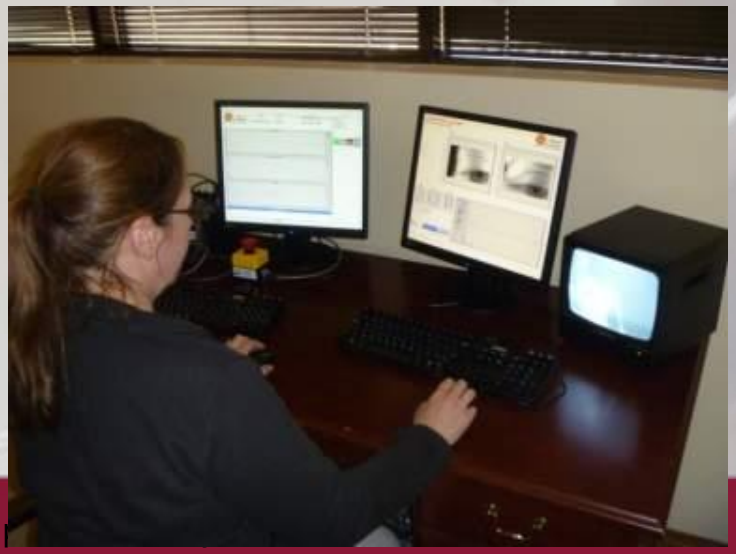


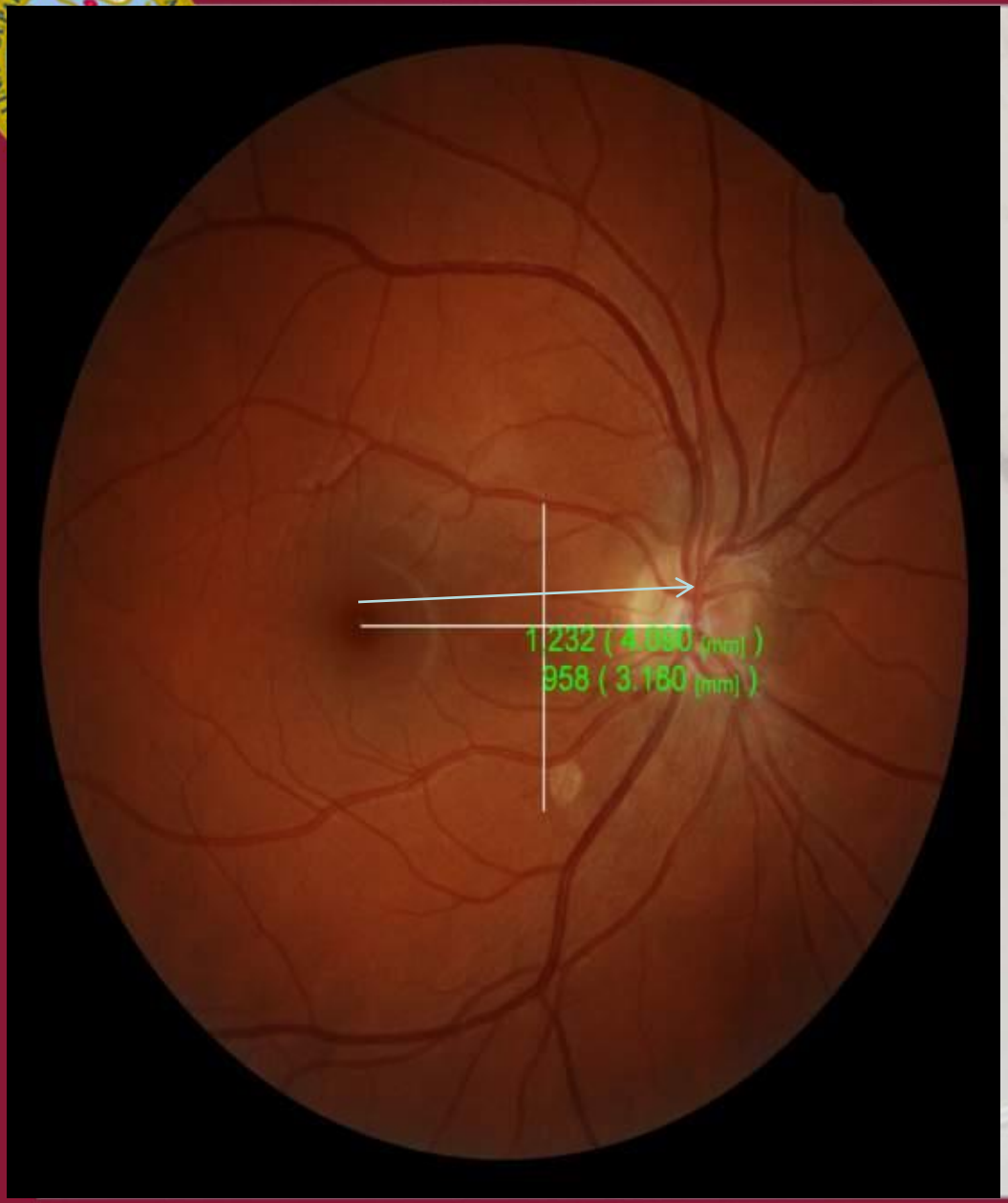
# OAC: Posturography/EEG Room

LTC Rob Price/ 719-503-7506/rob.price@us.arm

# OAC: Rotational Chair








## Fundus Photography

Non – invasive & quick

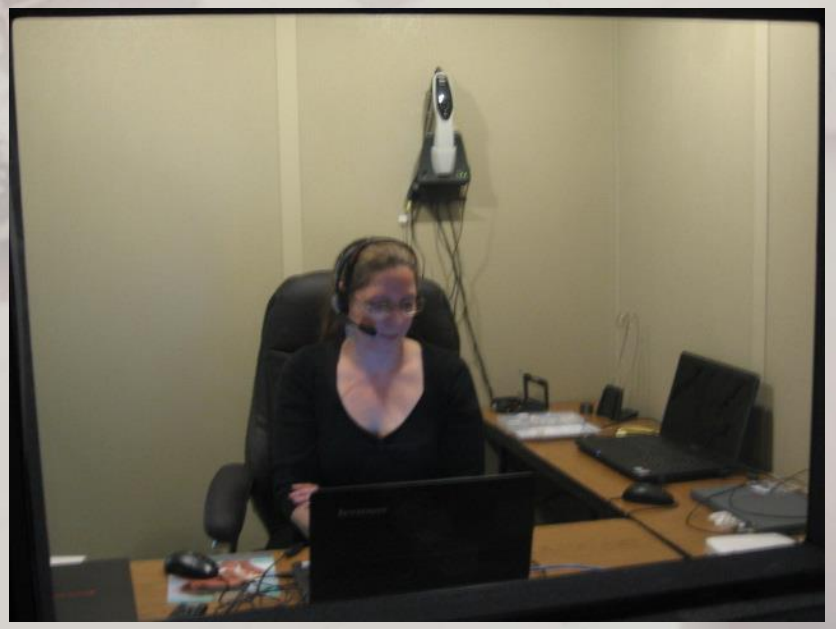
Measure the angle of ocular torsion from the fovea to the center of the blind spot referenced to Earth horizontal

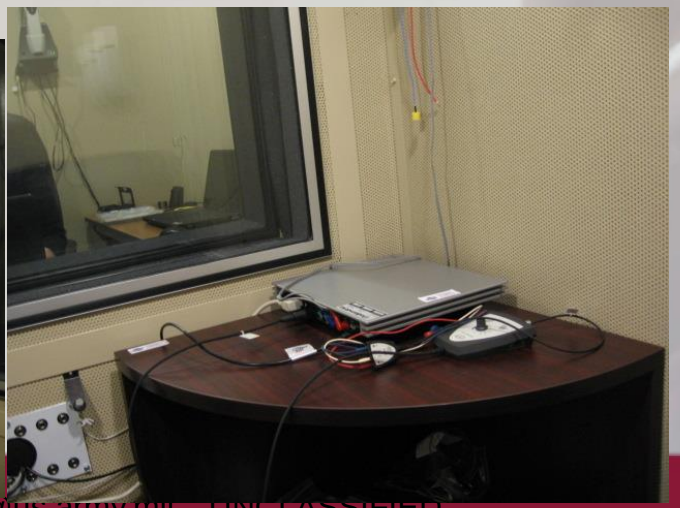
Normal orientation 2-6 degree

Abnormal ocular torsion > 6 degree

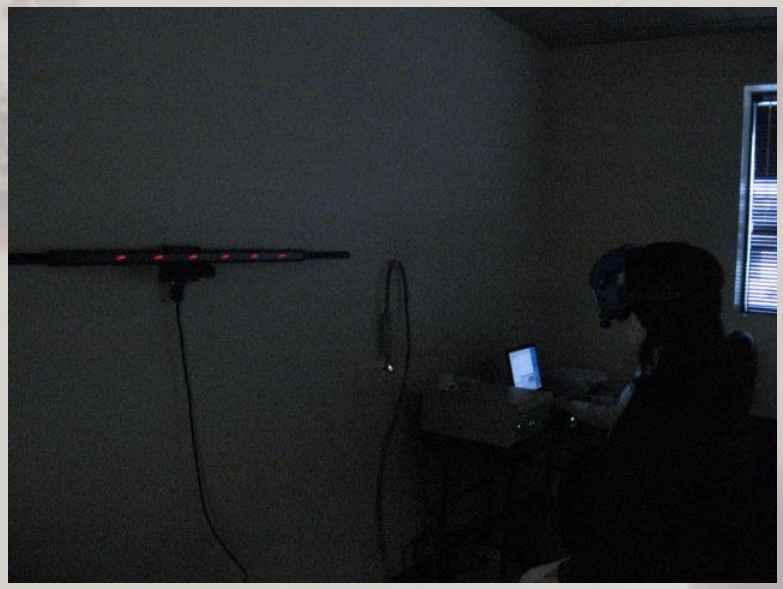
Seen as an acute reaction to utricle damage

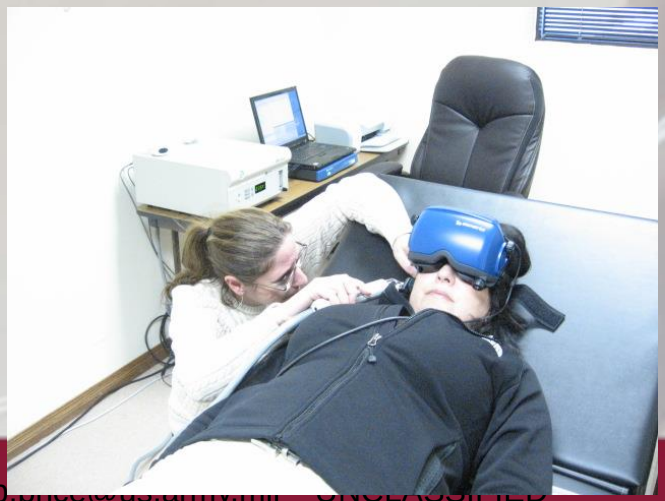
# OAC Sound Booth



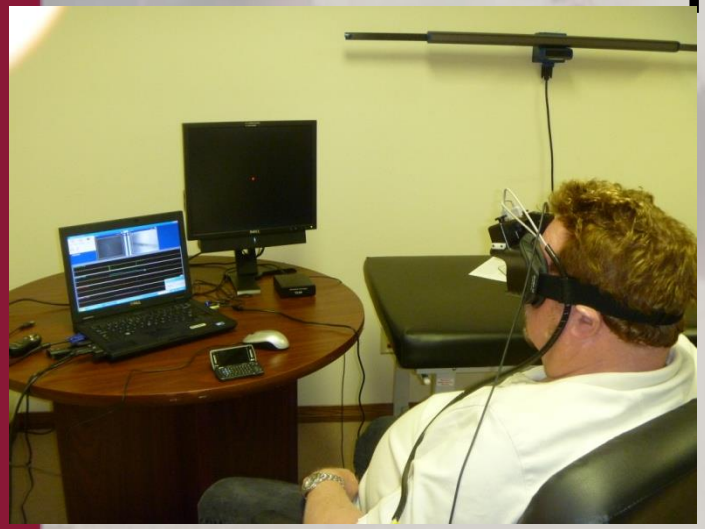


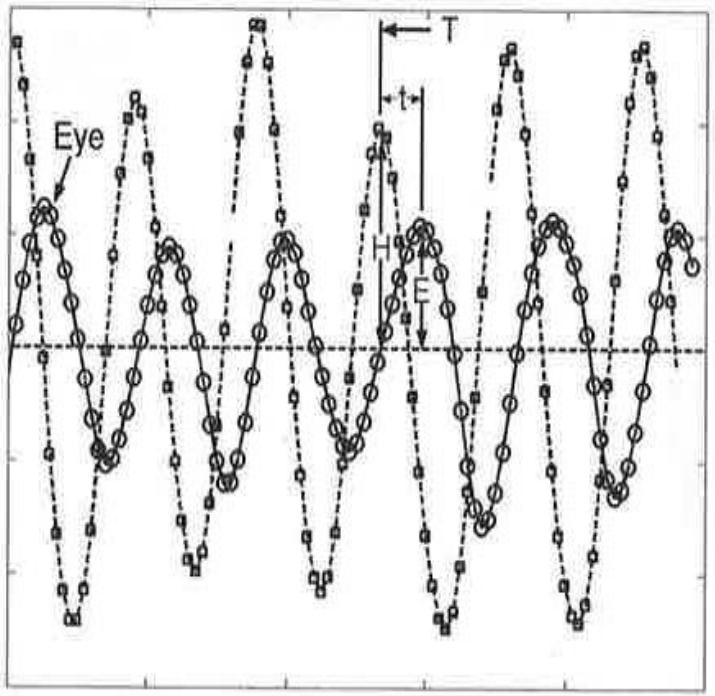
# OAC: VNG Room





# Auto head rotation: Vorteq; yaw and pitch






Jacobson & Shepard(2008)

# BIMA Screening & Enrollment

Initial contact to the SCC – 411

Pre-screen pass – 234

Randomized – 71

13 week f/u – 46

6 month f/u – 31

12 month f/u - 17

Goal: To have 60 with complete follow-up

# Confirming the TBI Event

- In theater notes on AHLTA-T(DoD EMR)
- Reported on Post Deployment Health Assessment (PDHA)
- Directive-Type Memorandum (DTM) 09-033
  - "Mandatory Events" reported as significant acts (SIGACTS) through operational channels to the Joint Trauma Analysis and Prevention of Injury in Combat (JTAPIC) program office
  - Medical guidance including command directed rest and use of Military Acute Concussion Evaluation (MACE) and a CPG
  - http://www.usaisr.amedd.army.mil/joint_trauma_system.html

# www.mods.army.mil

| home | help |

**MODS Applications**

- 68W
- AMEDD Human Resources
- ARTS
- CMS
- e-PROFILE
- EDUCATION
- EMS
- M3PT
- MEDPROS
- MHA (PHA/DHA/Referral Tracking)
- MWDE
- PBCT
- RC REPORTS
- SOF
- Soldier Patient Locator
- VOLUNTEER


MEDPROS WEB DATA ENTRY

Access MEDPROS Web Data Entry for completing Deployment Health Assessments. Web Data Entry is also used for completion of DA Form 7425 deployment requirements and Physical Exam Data Entry.

MODS
MEDICAL OPERATIONAL DATA SYSTEM

## Getting Started

- What is MODS?
- How do I register for MODS applications?
- How do I register for an AKO account?
- How do I reset my AKO account?
- Who do I contact for help?

## News and Events

- UM: Need access to a MODS application? - 05/29/2012
- CMS: CMS offers customized User Books - 05/15/2012
- BHDPManagement: BHDP application begins pilot testing - 05/01/2012

View All News and Events

## Army Links

- AKO - Army Knowledge Online
- Army Medicine
- ARNG
- U.S. Army Home Page
- AMEDD C & S
- Defense Link - DoD Home Page
- Tricare Homepage
- DENCOM
- MILVAX
- USAR - U.S. Army Reserve
- HRC Homepage
- AMAP - Army Medical Action Plan

MEDPROS - Windows Internet Explorer

https://medpros.mods.army.mil/MWDENet/

Favorites

MEDPROS

U.S.ARMY

ARMY STRONG

Home Privacy and Security

LOGIN WITH CAC

AKO ARMY KNOWLEDGE ONLINE

Bandwidth

(•) High ( ) Low

MEDPROS FORCE HEALTH PROTECTION

WHAT IS MWDE?

REGISTER FOR AN AKO ACCOUNT

CAC LOGIN PROCEDURE

RESET MY AKO PASSWORD

OBTAIN A MWDE ACCOUNT

MWDE RELATED LINKS

MEDPROS CONTACTS

New DD Forms for MEDPROS Access (both forms required)

## Welcome To MWDE

The Army Medical Department (AMEDD) developed the MEDPROS Web Data Entry (MWDE) module to provide a secure, online data entry portal for the posting of all immunization, medical readiness, and deployability data for all Active and Reserve components of the Army as well as DA Civilians, contractors and others. It is a powerful tool allowing those with data entry access the capability to post Immunization and Medical Readiness information updates directly into MEDPROS as they occur. It also incorporates the feed of a Soldier's Medical/Dental/Vision readiness status to the U.S. Army Forces Command's (FORSCOM) Deployment and Reconstitution Tracking System's (DARTS) automated DA Form 7425 (Sections IX Medical, X Dental, and XI Vision). For those with special access (granted separately), MWDE has built in links to the new Medical Health Assessment Module (for completion of Periodic and Deployment Health Assessments) and the eProfile Module (for the posting of both Temporary and Permanent Physical Profile PULHES and applicable Profile Codes).

Commander's and Medical leaders at various echelons are responsible for identifying and approving those who will

MWDE Session Timeout: 19 Min 50 Sec - Windows Internet Explorer

https://medpros.mods.army.mil/MWDEnet/Home/Default.aspx

Favorites

MWDE Session Timeout: 19 Min 50 Sec

MEDPROS
FORCE HEALTH PROTECTION

Home | SRP Processing | Data Entry | Medical Readiness | MWDE Reports | Administration | Help/L

Immunization | Individual

Deployment Health Assessments | Mass

SPFTCCO10 | Type SSN or Scan ID Card | Enter SSN | SSN: 9552 Name: PRICE ROBERT CHARLES Rank: LTC DOB: 1972/07/07 UIC: W2P1AA Gender: M

## MWDE UPDATES

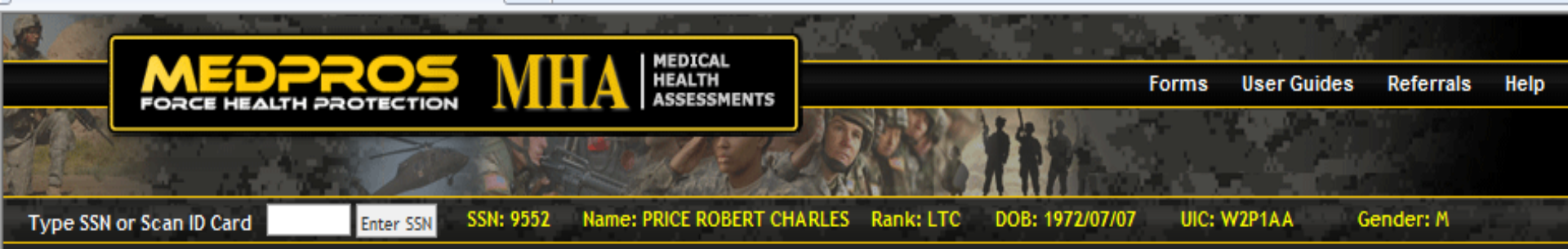
Latest Message - 2012/09/07

**Changes Coming for Web Reporting, Mainframe, and MWDE**

**On 11 Sep 2012, MEDPROS will be moving several changes into its production programs. The changes impact Web Reporting, Mainframe, and MWDE applications and are explained in detail in the PDF file available at this link.**

**The Web Reporting changes include a significant reorganization of the menu layout for accessing medical readiness reports, including renaming the DHA tab to MHA and moving the PHA and NCAT reports under that menu. The Medical Readiness tab has the most significant changes with**

https://medpros.mods.army.mil/MWDEnet/external.aspx




Type SSN or Scan ID Card | Enter SSN | SSN: 9552 | Name: PRICE ROBERT CHARLES | Rank: LTC | DOB: 1972/07/07 | UIC: W2P1AA | Gender: M

# Medical Health Assessments

Return to MWDE

Pre Deployment DD2795 | Post Deployment DD2796 | Post Deployment Health Reassessment DD2900 | NCA Tracking | PHA

## Post Deployment Health Assessment for: PRICE ROBERT CHARLES

Post-Deployment Survey

Indicates Forms Completed using the DD From 2796 April 2003 version.

Indicates Forms Completed using the DD From 2796 January 2008 version.

| | | Start Date | Last Updated Date | Status | |
|---|---|---|---|---|---|
| View Form | | 2/3/2010 11:21:00 AM | Feb 3 2010 11:21AM | Completed | Edit And Resign |
| 1/1/0001 12:00:00 AM | | No Post-Deployment 200304 Survey on file | | | |

Start New Survey

FOR OFFICIAL USE ONLY - Privacy Act Information

Done

| | | | | | |
|---|---|---|---|---|---|
| Skin diseases or rashes | No Yes | No Yes | No Yes | No Yes | No Yes |
| Other (please list): | No Yes | No Yes | No Yes | No Yes | No Yes |

**9.a. During this deployment, did you experience any of the following events? (Mark all that apply)**

(1) Blast or explosion (IED, RPG, land mine, grenade, etc.) No Yes

(2) Vehicular accident/crash (any vehicle, including aircraft) No Yes

(3) Fragment wound or bullet wound above your shoulders No Yes

(4) Fall No Yes

(5) Other event (for example, a sports injury to your head). No Yes

Describe:

**9.b. Did any of the following happen to you, or were you told happened to you, IMMEDIATELY after any of the event(s) you just noted in question 9.a.? (Mark all that apply.)**

(1) Lost consciousness or got "knocked out" No Yes

(2) Felt dazed, confused, or "saw stars" No Yes

(3) Didn't remember the event No Yes

(4) Had a concussion No Yes

(5) Had a head injury No Yes

**9.c. Did any of the following problems begin or get worse after the event(s) you noted in question 9.a.? (Mark all that apply.)**

(1) Memory problems or lapses No Yes

(2) Balance problems or dizziness No Yes

(3) Ringing in the ears No Yes

(4) Sensitivity to bright light No Yes

(5) Irritability No Yes

(6) Headaches No Yes

(7) Sleep problems No Yes

**9.d. In the past week, have you had any of the symptoms you indicated in 9.c.? (Mark all that apply.)**

(1) Memory problems or lapses No Yes

(2) Balance problems or dizziness No Yes

(3) Ringing in the ears No Yes

(4) Sensitivity to bright light No Yes

(5) Irritability No Yes

(6) Headaches No Yes

(7) Sleep problems No Yes

PRINT VIEW | PRINT RECORD | PRINT PHA | PREVIOUS | NEXT

# DTM 09-033 Requirements

- **Specific Guidance to Commanders (Injured/HEADS/< 50 meters)**
  - H – Headaches and/or Vomiting (Yes/No)
  - E – Ears ringing (Yes/No)
  - A – Amnesia and/or altered consciousness and/or loss of consciousness (Yes/No)
  - D – Double vision and/or dizziness (Yes/No)
  - S – Something feels wrong or is not right (Yes/No)

- **Specific Guidance to providers/medics**
  - C – Cognitive score (reported with 30 point score)
  - N – Neurological exam (reported as “Green” (normal) or “Red” (abnormal))
  - S – Symptoms reported as “A” (none reported) or “B” (at least one symptom reported).
  - MACE screening evaluation can be “24/Red/B” indicating a cognitive score of 24, abnormal neurological examination, and patient reporting presence of at least one symptom
  - Dispositions developed based on “Return to Play” guidelines from the Sports Medicine concussion literature

# Recruiting

- Ensure Command support
  - Warfighters and MTF
- Flyers, posters, TBI advocacy groups
- E-mail contact of Soldiers who screened positive at the SRC paid the largest dividends
- Provider to provider/ancillary staff
  - Grand rounds, monthly/quarterly training meetings, RESPECT-MIL, case managers


http://www.usammda.army.mil/HBO2.html

# $HBO_2$ for post concussive symptoms following mild TBI

**BOTTOM LINE**

- $HBO_2$ for PCS from mTBI is investigational
- HBO appears equivalent to breathing air at 1.2 ATA x 1 hour (sham)
- Chamber exposures may improve outcomes:
  - Placebo effects
  - Hawthorne effects
  - Therapeutic to visit the chamber daily
  - Doubtful that air at 1.2 ATA is “therapeutic” for chronic brain injury, but……If it is, mechanisms are unknown
- Complete BIMA (negotiating for annual follow up beyond 1 year) and obtain annual follow up to 2 years of DoD RCT participants
- Await published results from BIMA, NORMAL, LTFU, Dr. Harch’s study at LSU
- Phase III trials are not planned at this time, but BIMA results……

# More Research on mTBI

**Products/Devices**

- Cranial nerve stimulation
- Standards for helmet

**Pharmaceuticals**

- FDA-approved drugs or combinations
- New pharmaceuticals under development

**Alternative Therapeutics**

- Nutraceuticals, such as vitamins and essential nutrients
- Nutritional approaches, such as high protein (e.g. ketogenic) diets
- Improvements in rehabilitation techniques
- Acupuncture

**Objective Assessment Tools**

- Blast impact sensors
- Eye tracking tools
- Biomarker blood tests
- Neuroimaging

# Acknowledgements


MRMC Multicenter Study

USAMMDA

Walter Reed Army Institute of Research

Evans Army Community Hosp/10th SF Group

4th Infantry Division, Ft. Carson

Naval Hospital Camp Lejeune

Naval Hospital Camp Pendleton

Eisenhower Army Medical Center

LDS Hospital/University of Utah

Denver VAMC/Center of Mental Illness Research

Henry M. Jackson Foundation

EmpiriStat Inc.

OxyHeal Health Group

**Dr. Lin Weaver, LDS Hospital/University of Utah**

**Ms. Sue Churchill, LDS Hospital/University of Utah**

**COL R. Scott Miller, MRMC/USHSU**

**LTC Austin Chheu, PMO/USAMMDA**

Mr. Kyle Martin, PMO/USAMMDA

Ms. Christie Lawrence, PMO/USAMMDA

**COL(R) Heidi Terrio/American Lake VA/Tacoma, WA**

Dr. Paul Savage, JBLM, WA

Dr. Lisa Brenner, MIRECC , Denver VAMC

Dr. Nazanin Bahraini, MIRECC , Denver VAMC

Ms. Leah Russell, MIRECC , Denver VAMC

Ms. Maria Devore, MIRECC , Denver VAMC

**Capt Laura Grogan, Evans Army Community Hospital**

LCDR Virginia Skiba, Naval Hospital Camp Lejeune

CPT Corinna Bartos, Naval Hospital Camp Lejeune

LCDR Jason Gordon, Naval Hospital Camp Lejeune

CDR Jim Caviness, Naval Hospital Camp Pendleton


Questions???

# References


1. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010).
2. Department of Veterans Affairs, Department of Defense. VA/DoD Clinical Practice Guideline for Management of Concussion/Mild Traumatic Brain Injury (mTBI) version 1.0 2009.
3. Deputy Director of Defense: Directive-Type Memorandum (DTM) 09-033, “Policy Guidance for Management of Concussion/Mild Traumatic Brain Injury in the Deployed Setting”. June 21, 2010. *Incorporating Change 3, November 7, 2011.*