Evidence Brief: Hyperbaric Oxygen Therapy for Traumatic Brain Injury and/or Post-traumatic Stress Disorder

Supplemental Materials

July 2021

Prepared for:

Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service
Washington, DC 20420

Prepared by:

Evidence Synthesis Program (ESP) Coordinating Center
Portland VA Health Care System
Portland, OR
Mark Helfand, MD, MPH, MS, Director

Authors:

Nicholas J. Parr, PhD, MPH
Johanna Anderson, MPH
Stephanie Veazie, MPH

U.S. Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service

TABLE OF CONTENTS

APPENDIX A: UHMS INDICATIONS FOR HBOT

UHMS Clearances[1]
1. Air or Gas Embolism
2. Carbon Monoxide Poisoning or Carbon Monoxide Poisoning Complicated by Cyanide Poisoning
3. Clostridal Myositis and Myonecrosis (Gas Gangrene)
4. Crush Injury, Compartment Syndrome, and other Acute Traumatic Ischemias
5. Decompression Sickness
6. Enhancement of Healing in Selected Problem Wounds
7. Exceptional Blood Loss (Anemia)
8. Intracranial Abscess
9. Necrotizing Soft Tissue Infections
10. Osteomyelitis (Refractory)
11. Delayed Radiation Injury (Soft Tissue and Bony Necrosis)
12. Skin Grafts & Flaps (Compromised)
13. Thermal Burns
14. Idiopathic Sudden Sensorineural Hearing Loss[2]

Abbreviation. UHMS=Undersea & Hyperbaric Medical Society

APPENDIX B: GUIDELINES ON HBOT USE

Organization Year	Title	Comments on HBOT in relation to TBI and/or PTSD
VA/DOD 2017[3]	Clinical Practice Guideline for The Management of Posttraumatic Stress Disorder and Acute Stress Disorder	"There is no conclusive evidence that HBOT is effective for treating PTSD. There have been no RCTs or uncontrolled trials specifically focused on patients with PTSD, and there is disagreement about what constitutes an adequate sham treatment. In a DoD study, 72 soldiers with TBI (66% with PTSD) were randomized to standard care (78%), HBOT (54%), or sham HBOT (64%). Baseline scores on the PCL were less severe than in all-PTSD studies, likely because not everyone had PTSD. Scores were still in the severe range. Based on the evidence to date, and the practical and cost concerns, it does not appear that HBOT is a promising treatment for further study." "There is insufficient evidence to recommend for or against the following somatic therapies: repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), hyperbaric oxygen therapy (HBOT), stellate ganglion block (SGB), or vagal nerve stimulation (VNS)."
VA/DOD 2016[4] (update in progress)	Clinical Practice Guideline for The Management of Concussion-mild Traumatic Brain Injury	NA
Colorado Division of Workers' Compensation 2012[5]	Traumatic Brain Injury Medical Treatment Guidelines	"Despite evidence of limited physiological changes with hyperbaric oxygen, there is insufficient evidence to suggest that hyperbaric oxygen would functionally benefit stroke or TBI patients. Complications can occur, including tension pneumothorax. Hyperbaric oxygen is not recommended acutely or chronically. Ongoing studies could affect this recommendation."
Brain Trauma Foundation 2017[6]	Guidelines for the Management of Severe Traumatic Brain Injury, 4th Edition	Excluded studies on HBOT
Tenth European Consensus Conference on Hyperbaric Medicine 2017[7]	Tenth European Consensus Conference on Hyperbaric Medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment	It would be reasonable to consider HBOT in acute moderate-severe traumatic brain injury (TBI) patients and in a highly selected group of patients with chronic TBI who have clear evidence of metabolically dysfunctional brain region(s) (Type 3 recommendation, Grade C level of evidence) We recommend HBOT use in TBI to be used only in the context of an investigational study protocol approved by an ethics committee and performed according to clinical research good practice (Type 1 Recommendation, Grade A level of evidence)

APPENDIX C: SEARCH STRATEGIES

1. Search for current systematic reviews (limited to 2012 forward) **Date Searched: 10/07/20**	
Sources:	**Evidence:**
AHRQ	Search: hyperbaric; HBOT Relevant Results: None
CADTH	Search: hyperbaric; HBOT Relevant Results: CADTH. (2020). Hyperbaric Oxygen Therapy for the Treatment of Chronic Pain: A Review of Clinical Effectiveness and Cost-Effectiveness. Rapid Response. Ottawa, CAN.
NICE	Search: (hyperbaric) AND (post-traumatic stress or PTSD or brain injury or TBI); (HBOT) AND (post-traumatic stress or PTSD or brain injury or TBI) Relevant Results: None
ECRI Institute	Search: hyperbaric; HBOT Relevant Results: ECRI Institute. (2017). VA/DoD clinical practice guideline for the management of posttraumatic stress disorder and acute stress disorder.
VA Products: VATAP, PBM, HSR&D publications, VA ART Database	A. http://www.hsrd.research.va.gov/research/default.cfm Search: hyperbaric; HBOT Relevant Results: None B. http://www.research.va.gov/research_topics/ Relevant Results: None
MEDLINE: Systematic Reviews	Database: Ovid MEDLINE(R) ALL 1946 to October 12, 2020 Search Strategy: --- 1 (hyperbaric or HBOT).mp. (18029) 2 exp Hyperbaric Oxygenation/ (11866) 3 1 or 2 (18029) 4 exp stress disorders, post-traumatic/ (33123) 5 exp combat disorders/ (3135) 6 (post-traumatic stress or posttraumatic stress or PTSD).mp. (41197) 7 exp craniocerebral trauma/ (159475) 8 exp Glasgow Coma Scale/ (9571)

	9 exp Glasgow Outcome Scale/ (2015) 10 (mTBI or TBI).mp. (29025) 11 ((brain* or capitis or cerebr* or crani* or hemispher* or inter-crani* or intra-crani* or skull*) adj4 (contusion* or damag* or fractur* or injur* or trauma* or wound* or concuss*)).mp. (192159) 12 concuss*.mp. (14300) 13 diffuse axonal injur*.mp. (1710) 14 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (21045) 15 Ranchos Los Amigos Scale.mp. (4) 16 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (320212) 17 3 and 16 (815) 18 limit 17 to english language (672) 19 limit 18 to yr="2017 -Current" (135) 20 (systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/) or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or cijntion.tw. or cijntions.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment outcome/ or treatment outcome.tw. or pmcbook.mp.))) not (letter or newspaper article).pt. (445238) 21 "Review"/ or "Review Literature as Topic"/ (2824729) 22 20 or 21 (3050721) 23 19 and 22 (27) **********
PsycINFO	Database: APA PsycInfo 1806 to October Week 1 2020 Search Strategy: --- 1 (hyperbaric or HBOT).mp. (459) 2 exp Posttraumatic Stress Disorder/ (33541) 3 exp COMBAT EXPERIENCE/ (2946) 4 (post-traumatic stress or posttraumatic stress or PTSD).mp. (50977) 5 exp Traumatic Brain Injury/ (19869) 6 exp Brain Damage/ (17778) 7 exp Head Injuries/ (6614) 8 (mTBI or TBI).mp. (12642)

	9 ((brain* or capitis or cerebr* or crani* or hemispher* or inter-crani* or intra-crani* or skull*) adj4 (contusion* or damag* or fractur* or injur* or trauma* or wound* or concuss*)).mp. (56650) 10 concuss*.mp. (4059) 11 diffuse axonal injur*.mp. (435) 12 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (6230) 13 Ranchos Los Amigos Scale.mp. (11) 14 or/2-13 (110962) 15 1 and 14 (102) 16 (systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/) or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or cijntion.tw. or cijntions.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment outcome/ or treatment outcome.tw. or pmcbook.mp.))) not (letter or newspaper article).pt. (135282) 17 "Review"/ or "Review Literature as Topic"/ (22719) 18 16 or 17 (155525) 19 15 and 18 (10) 20 limit 19 to english language (9) 21 limit 20 to yr="2017 -Current" (5) **********
Cochrane Database of Systematic Reviews & Cochrane Methodology Register	Database: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to October 1, 2020 Search Strategy: ---------- 1 (hyperbaric or HBOT).mp. (95) 2 (post-traumatic stress or posttraumatic stress or PTSD).mp. (234) 3 (mTBI or TBI).mp. (76) 4 ((brain* or capitis or cerebr* or crani* or hemispher* or inter-crani* or intra-crani* or skull*) adj4 (contusion* or damag* or fractur* or injur* or trauma* or wound* or concuss*)).mp. (679) 5 concuss*.mp. (51) 6 diffuse axonal injur*.mp. (38) 7 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (125) 8 Ranchos Los Amigos Scale.mp. (0)

	9 or/2-8 (966) 10 1 and 9 (17) 11 limit 10 to last 2 years (3) **********
Systematic Reviews (Journal)	Search: hyperbaric; HBOT Relevant Results: None

2. Systematic reviews currently under development (forthcoming reviews & protocols) Date Searched: 10/07/20	
Sources:	**Evidence:**
PROSPERO (SR registry)	http://www.crd.york.ac.uk/PROSPERO/ Search: Hyperbaric; HBOT Relevant Results: None
DoPHER (SR Protocols)	Search: Hyperbaric; HBOT Relevant Results: None

3. Current Guidelines Date Searched: 10/07/20	
Sources:	**Evidence:**
VA/DoD Clinical Practice Guidelines	Relevant Results:
National Guideline Clearinghouse No longer exists	
Google Scholar	Search: “"hyperbaric oxygen therapy" guideline; HBOT guideline Relevant Results: None
Epistemonikos	Search: (title:(hyperbaric or HBOT) OR abstract:(hyperbaric or HBOT)) AND (title:(PTSD) OR abstract:(PTSD)) OR (title:(post-traumatic stress) OR abstract:(post-traumatic stress)) OR (title:(TBI) OR abstract:(TBI)) AND (title:(brain injury) OR abstract:(brain injury)) Relevant Results: None

TRIP	Search: (hyperbaric or HBOT) AND (post-traumatic stress or PTSD or brain injury or TBI) Relevant Results: None
Medline: Guideline Search	Database: Ovid MEDLINE(R) ALL 1946 to October 01, 2020 Search Strategy: --- 1 (hyperbaric or HBOT).mp. (17557) 2 exp Hyperbaric Oxygenation/ (11854) 3 1 or 2 (17557) 4 exp stress disorders, post-traumatic/ (33058) 5 exp combat disorders/ (3134) 6 (post-traumatic stress or posttraumatic stress or PTSD).mp. (38761) 7 exp craniocerebral trauma/ (159275) 8 exp Glasgow Coma Scale/ (9560) 9 exp Glasgow Outcome Scale/ (2010) 10 (mTBI or TBI).mp. (27441) 11 ((brain* or capitis or cerebr* or crani* or hemispher* or inter-crani* or intra-crani* or skull*) adj4 (contusion* or damag* or fractur* or injur* or trauma* or wound* or concuss*)).mp. (185930) 12 concuss*.mp. (13501) 13 diffuse axonal injur*.mp. (1640) 14 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (20135) 15 Ranchos Los Amigos Scale.mp. (4) 16 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (310598) 17 3 and 16 (788) 18 limit 17 to english language (645) 19 exp GUIDELINE/ (34662) 20 guideline*.mp. (484539) 21 19 or 20 (484539) 22 18 and 21 (11) 23 limit 22 to yr=”2018-Current” (1) **********
UpToDate	Search: Hyperbaric; HBOT Relevant Results: https://www.uptodate.com/contents/hyperbaric-oxygen-therapy

4. Current primary literature (limited to 2014 forward) Date Searched: 10/07/20	
Sources:	**Search Strategy/ Evidence:**
Medline	Database: Ovid MEDLINE(R) ALL 1946 to October 12, 2020 Search Strategy: --- 1 (hyperbaric or HBOT).mp. (18029) 2 exp Hyperbaric Oxygenation/ (11866) 3 1 or 2 (18029)

	4 exp stress disorders, post-traumatic/ (33123) 5 exp combat disorders/ (3135) 6 (post-traumatic stress or posttraumatic stress or PTSD).mp. (41197) 7 exp craniocerebral trauma/ (159475) 8 exp Glasgow Coma Scale/ (9571) 9 exp Glasgow Outcome Scale/ (2015) 10 (mTBI or TBI).mp. (29025) 11 ((brain* or capitis or cerebr* or crani* or hemispher* or inter-crani* or intra-crani* or skull*) adj4 (contusion* or damag* or fractur* or injur* or trauma* or wound* or concuss*)).mp. (192159) 12 concuss*.mp. (14300) 13 diffuse axonal injur*.mp. (1710) 14 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (21045) 15 Ranchos Los Amigos Scale.mp. (4) 16 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (320212) 17 3 and 16 (815) 18 limit 17 to english language (672) 19 limit 18 to yr="2017 -Current" (135) **********
Medline: Harms	Database: Ovid MEDLINE(R) ALL 1946 to October 12, 2020 Search Strategy: --- 1 (hyperbaric or HBOT).mp. (18029) 2 exp Hyperbaric Oxygenation/ (11866) 3 1 or 2 (18029) 4 exp stress disorders, post-traumatic/ (33123) 5 exp combat disorders/ (3135) 6 (post-traumatic stress or posttraumatic stress or PTSD).mp. (41197) 7 exp craniocerebral trauma/ (159475) 8 exp Glasgow Coma Scale/ (9571) 9 exp Glasgow Outcome Scale/ (2015) 10 (mTBI or TBI).mp. (29025) 11 ((brain* or capitis or cerebr* or crani* or hemispher* or inter-crani* or intra-crani* or skull*) adj4 (contusion* or damag* or fractur* or injur* or trauma* or wound* or concuss*)).mp. (192159) 12 concuss*.mp. (14300) 13 diffuse axonal injur*.mp. (1710) 14 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (21045) 15 Ranchos Los Amigos Scale.mp. (4) 16 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (320212) 17 3 and 16 (815) 18 exp Patient Harm/ (170) 19 harm*.mp. (200920) 20 exp Long Term Adverse Effects/ (584) 21 adverse effect*.mp. (1870268) 22 18 or 19 or 20 or 21 (2047778) 23 17 and 22 (119) 24 limit 23 to english language (106) 25 limit 24 to yr=”2017-Current” (11) **********
PsychINFO	Database: APA PsycInfo 1806 to September Week 4 2020 Search Strategy: ---

	1 (hyperbaric or HBOT).mp. (459) 2 exp Posttraumatic Stress Disorder/ (33509) 3 exp COMBAT EXPERIENCE/ (2944) 4 (post-traumatic stress or posttraumatic stress or PTSD).mp. (50917) 5 exp Traumatic Brain Injury/ (19844) 6 exp Brain Damage/ (17776) 7 exp Head Injuries/ (6608) 8 (mTBI or TBI).mp. (12631) 9 ((brain* or capitis or cerebr* or crani* or hemispher* or inter-crani* or intra-crani* or skull*) adj4 (contusion* or damag* or fractur* or injur* or trauma* or wound* or concuss*)).mp. (56614) 10 concuss*.mp. (4049) 11 diffuse axonal injur*.mp. (434) 12 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (6225) 13 Ranchos Los Amigos Scale.mp. (11) 14 or/2-13 (110860) 15 1 and 14 (102) 16 limit 15 to english language (98) 17 limit 16 to yr="2014 -Current" (14) **********
CCRCT	Database: EBM Reviews - Cochrane Central Register of Controlled Trials September 2020 Search Strategy: --- 1 (hyperbaric or HBOT).mp. (3105) 2 exp Hyperbaric Oxygenation/ (373) 3 1 or 2 (3105) 4 exp stress disorders, post-traumatic/ (2607) 5 exp combat disorders/ (134) 6 (post-traumatic stress or posttraumatic stress or PTSD).mp. (6169) 7 exp craniocerebral trauma/ (3291) 8 exp Glasgow Coma Scale/ (452) 9 exp Glasgow Outcome Scale/ (149) 10 (mTBI or TBI).mp. (2923) 11 ((brain* or capitis or cerebr* or crani* or hemispher* or inter-crani* or intra-crani* or skull*) adj4 (contusion* or damag* or fractur* or injur* or trauma* or wound* or concuss*)).mp. (10192) 12 concuss*.mp. (859) 13 diffuse axonal injur*.mp. (74) 14 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (2752) 15 Ranchos Los Amigos Scale.mp. (1) 16 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (19409) 17 3 and 16 (146) 18 limit 17 to english language (86) 19 limit 18 to yr="2017 -Current" (29) **********
Pedro	Search: Hyperbaric; HBOT (limited to 2018 forward) Relevant Results: None

PTSDpubs	Search: (hyperbaric OR HBOT) AND (post-traumatic stress OR PTSD OR brain injury OR TBI) Relevant Results: None

5. Primary literature currently under development (forthcoming studies & protocols) Date Searched: 10/07/20	
Sources:	**Search Strategy/ Evidence:**
Clinicaltrials.gov	Search: Hyperbaric or HBOT Relevant Results: None
UK Clinical Trials Gateway	Search: Hyperbaric; HBOT Relevant results: None
WHO International Clinical Trials Registry Platform	Search: Hyperbaric or HBOT Relevant results: None

6. Advocacy Groups (HBOT, PTSD, and TBI) Date Searched: 10/07/20	
Sources:	**Search Strategy/ Evidence:**
Brain Injury Association of America	Search: hyperbaric; HBOT Relevant Results: None
Kessler Foundation	Search: hyperbaric; HBOT Relevant Results: None
Concussion Legacy Foundation	Search: hyperbaric; HBOT Relevant Results: None

San Diego Brain Injury Foundation	Search: hyperbaric; HBOT Relevant Results: None
Neuro-Laser Foundation	Relevant Results: None
PTSD Foundation of America	Relevant Results: None
National Center for PTSD	Search: hyperbaric; HBOT Relevant Results: None
The official website of the Military Health System and the Defense Health Agency	Search: hyperbaric; HBOT Relevant Results: Hyperbaric Oxygen Therapy for Mild Traumatic Brain Injury. (2018) HR 3326 5.2.2011
PTSD Alliance	Relevant Results: None
International Hyperbaric Medical Foundation	Relevant Results: None
International Hyperbaric Medical Association	Relevant Results: None
HBOT2017 Conference & Expo	Relevant Results: None
HBOT.com	Relevant Results: None
HBOT for Vets	Relevant Results: None
HBOT in Wound Care	Relevant Results: None
Undersea & Hyperbaric Medical Society	https://www.uhms.org/resources/hbo-indications.html Relevant Results: None

Free The Chamber	Relevant Results: None
Holistic Hyperbaric	Relevant Results: None
Harch Hyperbarics Media	Relevant Results: None
Hyperbaric Link	Relevant Results: None
The American Legion	Relevant Results: None
Treat Now	Relevant Results: None

7. Search for current systematic reviews looking at the effectiveness of interventions (other than HBOT) for PTSD or TBI (limited to 2012 forward) **Date Searched: 12-14-20**	
Sources:	**Evidence:**
AHRQ	Search: post-traumatic stress disorder; traumatic brain injury Relevant Results: Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder. November 2020. Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder: A Systematic Review Update. May 2018. Interventions for the Prevention of Posttraumatic Stress Disorder (PTSD) in Adults After Exposure to Psychological Trauma. April 2013. Multidisciplinary Postacute Rehabilitation for Moderate to Severe Traumatic Brain Injury in Adults. June 2012.
CADTH	Search: post-traumatic stress disorder; traumatic brain injury Relevant Results: CADTH Results for PTSD (n=52) CADTH Results for TBI (n=44)
NICE	Search: (post traumatic stress disorder OR traumatic brain injury OR TBI OR PTSD) AND (treatment OR intervention OR program) Relevant Results:

	Prevalence, assessment, and treatment of mild traumatic brain injury and posttraumatic stress disorder: a systematic review of the evidence. 2014. Acupuncture for posttraumatic stress disorder : a systematic review of randomized controlled trials and prospective clinical trials. 2013.
ECRI Institute	Search: post-traumatic stress disorder; traumatic brain injury Relevant Results: Search results in separate document
VA Products: VATAP, PBM, HSR&D publications, VA ART Database	A. http://www.hsrd.research.va.gov/research/default.cfm Search: post-traumatic stress disorder; traumatic brain injury Relevant Results: Treatment Variation and Treatment Effectiveness in Veterans with PTSD. 2016. Telerehabilitation for OIF/OEF Returnees with Combat-Related Traumatic Brain Injury. 2014. B. http://www.research.va.gov/research_topics/ Relevant Results: None
Cochrane Database of Systematic Reviews & Cochrane Methodology Register Cochrane Methodology Register not updated past 2012	Database: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 10, 2020 Search Strategy: --- 1 Therapeutics.kw. (49) 2 (therapy or therapies or treatment or treatments or intervention or interventions or program or programs or medication or medications or drug or drugs or pharmaceutical or pharmaceuticals or therapeutic or therapeutics).mp. (10917) 3 1 or 2 (10917) 4 (post-traumatic stress or posttraumatic stress or PTSD).mp. (239) 5 (mTBI or TBI).mp. (78) 6 ((brain* or capitis or cerebr* or crani* or hemispher* or inter-crani* or intra-crani* or skull*) adj4 (contusion* or damag* or fractur* or injur* or trauma* or wound* or concuss*)).mp. (681) 7 concuss*.mp. (52) 8 diffuse axonal injur*.mp. (38) 9 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (127) 10 Ranchos Los Amigos Scale.mp. (0) 11 or/4-10 (975) 12 3 and 11 (973) 13 limit 12 to last 8 years (636) **********

APPENDIX D: LIST OF EXCLUDED STUDIES

Exclude reasons: 1=Ineligible population, 2=Ineligible intervention, 3=Ineligible comparator, 4=Ineligible outcome, 5=Ineligible timing, 6=Ineligible study design, 7=Ineligible publication type 8=Outdated or ineligible systematic review, E9=Non-English language, E10=Unable to locate full-text

#	Citation	Exclude reason
1	Adams E. Hyperbaric Oxygen Therapy for Traumatic Brain Injury and Post Traumatic Stress Disorder. *VA Technology Assessment Program.* 2010.	E8
2	Adamides AA, Winter CD, Lewis PM, Cooper DJ, Kossmann T, Rosenfeld JV. Current controversies in the management of patients with severe traumatic brain injury. ANZ J Surg. 2006;76(3):163-174.	E7
3	Algattas H, Huang JH. Neurotrauma and Repair Research: Traumatic Brain Injury (TBI) and its Treatments. Biomed. 2013;5:51-56.	E7
4	Algattas H, Huang JH. Traumatic Brain Injury pathophysiology and treatments: early, intermediate, and late phases post-injury. *Int.* 2013;15(1):309-341.	E7
5	Alternative Therapy Evaluation Committee for the Insurance Corporation of British C. A review of the scientific evidence on the treatment of traumatic brain injuries and strokes with hyperbaric oxygen. *Brain Injury.* 2003;17(3):225-236.	E8
6	Bennett MH. Evidence brief: hyperbaric oxygen therapy (HBOT) for traumatic brain injury and/or post-traumatic stress disorder. *Diving Hyperb Med.* 2018;48(2):115.	E7
7	Bennett MH. Hyperbaric medicine and the placebo effect. *Diving Hyperb Med.* 2014;44(4):235-240.	E7
8	Bennett MH, Mitchell SJ. Emerging indications for hyperbaric oxygen. *Current Opinion in Anaesthesiology.* 2019;32(6):792-798.	E7
9	Bennett MH, Trytko B, Jonker B. Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury. *Cochrane Database of Systematic Reviews.* 2004(4):CD004609.	E8*
10	Bennett MH, Trytko B, Jonker B. Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury. Cochrane Database of Systematic Reviews. 2012;12:CD004609.	E7
11	Beynon C, Kiening KL, Orakcioglu B, Unterberg AW, Sakowitz OW. Brain tissue oxygen monitoring and hyperoxic treatment in patients with traumatic brain injury. *Journal of Neurotrauma.* 2012;29(12):2109-2123.	E7
12	Brenner L, Bahraini N, Forster J. Neuropsychological outcomes from a Phase II, randomized, sham-controlled trial hyperbaric oxygen for post-concussion syndrome. *Brain injury.* 2017;Conference: 12th world congress on brain injury of the international brain injury association. United states. 31(6-7):805.	E7
13	Brenner L BNFJ. Neuropsychological outcomes from a Phase II, randomized, sham-controlled trial hyperbaric oxygen for post-concussion syndrome. Brain injury. 2017;31(6-7):805-.	E7
14	Brenner L, Bahraini N, Weaver L, et al. Effects of hyperbaric oxygen on symptoms and quality-of-life among US Military service members with persistent post-concussion symptoms: a randomized, double-blind, sham-controlled trial. *Brain injury.* 2016;Conference: 11th world congress on brain injury of the international	E7

#	Citation	Exclude reason
	brain injury association. Netherlands. Conference start:. 20160302. Conference end: 20160305 30(5-6):729.	
15	Canadian Agency for Drugs and Technologies in Health (CADTH). Hyperbaric oxygen therapy for adults with mental illness: a review of the clinical effectiveness. *Rapid Response.* 2014.	E8
16	Carney N, Totten AM, O'reilly C, et al. Guidelines for the management of severe traumatic brain injury. *Neurosurgery.* 2017;80(1):6-15.	E7
17	Churchill S, Miller RS, Deru K, Wilson SH, Weaver LK. Simple and Procedural Reaction Time for Mild Traumatic Brain Injury in a Hyperbaric Oxygen Clinical Trial. *Mil Med.* 2016;181(5 Suppl):40-44.	E4
18	Cifu DX, Hoke KW, Wetzel PA, Wares JR, Gitchel G, Carne W. Effects of hyperbaric oxygen on eye tracking abnormalities in males after mild traumatic brain injury. *J Rehabil Res Dev.* 2014;51(7):1047-1056.	E4*
19	Colorado Division of Workers' Compensation. Traumatic Brain Injury Medical Treatment Guidelines. 2012.	E7
20	Cossu G. Therapeutic options to enhance coma arousal after traumatic brain injury: state of the art of current treatments to improve coma recovery. *Br J Neurosurg.* 2014;28(2):187-198.	E4
21	Crawford C, Teo L, Yang E, Isbister C, Berry K. Is Hyperbaric Oxygen Therapy Effective for Traumatic Brain Injury? A Rapid Evidence Assessment of the Literature and Recommendations for the Field. *Journal of Head Trauma Rehabilitation.* 2017;32(3):E27-E37.	E8*
22	Daly S, Thorpe M, Rockswold S, et al. Hyperbaric Oxygen Therapy in the Treatment of Acute Severe Traumatic Brain Injury: A Systematic Review. *Journal of Neurotrauma.* 2018;35(4):623-629.	E8
23	Dong Y, Hu X, Wu T, Wang T. Erratum: Effect of hyperbaric oxygenation therapy on post-concussion syndrome. *Experimental & Therapeutic Medicine.* 2018;16(6):4918.	E8
24	Dong Y, Hu X, Wu T, Wang T. Effect of hyperbaric oxygenation therapy on post-concussion syndrome. Experimental & Therapeutic Medicine. 2018;16(3):2193-2202.	E8
25	ECRI Institute. Chambers, Hyperbaric. 2017.	E7
26	ECRI Institute. Hyperbaric Oxygen Therapy for Postconcussion Syndrome. 2016.	E8
27	ECRI Institute. Infusion Pumps to Consider for Use with Hyperbaric Chambers. 2016.	E2
28	ECRI Institute. Procurement Trends: Hyperbaric Chambers - May, 2016. 2016.	E7
29	Efrati S, Ben-Jacob E. Reflections on the neurotherapeutic effects of hyperbaric oxygen. *Expert rev.* 2014;14(3):233-236.	E7
30	Eve DJ, Steele MR, Sanberg PR, Borlongan CV. Hyperbaric oxygen therapy as a potential treatment for post-traumatic stress disorder associated with traumatic brain injury. *Neuropsychiatr.* 2016;12:2689-2705.	E7
31	Fife CE, Gelly H, Walker D, Eckert KA. Rapid analysis of hyperbaric oxygen therapy registry data for reimbursement purposes: Technical communication. *Undersea Hyperb Med.* 2016;43(6):633-639.	E7
32	Figueroa XA, Wright JK. Clinical results in brain injury trials using HBO2 therapy: Another perspective. *Undersea Hyperb Med.* 2015;42(4):333-351.	E7
33	Figueroa XA, Wright JK. Hyperbaric oxygen: B-level evidence in mild traumatic brain injury clinical trials. *Neurology.* 2016;87(13):1400-1406.	E7

#	Citation	Exclude reason
34	Figueroa XA, Wright JK. Author response: Hyperbaric oxygen: B-Level evidence in mild traumatic brain injury clinical trials. *Neurology.* 2017;89(7):750-751.	E10
35	Figueroa XA, Wright JK. "Hyperbaric oxygen: B-level evidence in mild traumatic brain injury clinical trials": Author's response. Neurology. 2017;89(7):750-751.	E7
36	Gajewski BJ, Berry SM, Barsan WG, et al. Hyperbaric oxygen brain injury treatment (HOBIT) trial: a multifactor design with response adaptive randomization and longitudinal modeling. *Pharm.* 2016;15(5):396-404.	E7
37	Guedes VA, Song S, Provenzano M, Borlongan CV. Understanding the pathology and treatment of traumatic brain injury and posttraumatic stress disorder: a therapeutic role for hyperbaric oxygen therapy. *Expert rev.* 2016;16(1):61-70.	E7
38	Hadanny A, Abbott S, Suzin G, Bechor Y, Efrati S. Effect of hyperbaric oxygen therapy on chronic neurocognitive deficits of post-traumatic brain injury patients: retrospective analysis. *BMJ Open.* 2018;8(9):e023387.	E6
39	Hadanny A, Efrati S. The efficacy and safety of hyperbaric oxygen therapy in traumatic brain injury. *Expert rev.* 2016;16(4):359-360.	E7
40	Hadanny A, Efrati S. Oxygen--a limiting factor for brain recovery. *Crit Care.* 2015;19:307.	E7
41	Hadanny A, Efrati S. Treatment of persistent post-concussion syndrome due to mild traumatic brain injury: current status and future directions. *Expert rev.* 2016;16(8):875-887.	E7
42	Hadanny A, Meir O, Bechor Y, Fishlev G, Bergan J, Efrati S. Seizures during hyperbaric oxygen therapy: retrospective analysis of 62,614 treatment sessions. *Undersea Hyperb Med.* 2016;43(1):21-28.	E1
43	Hampson NB, Holm J. "Hyperbaric oxygen: B-level evidence in mild traumatic brain injury clinical trials": Comment. *Neurology.* 2017;89(7):750.	E7
44	Harch PG. Hyperbaric oxygen in chronic traumatic brain injury: oxygen, pressure, and gene therapy. *Medical gas research.* 2015;5:9.	E7
45	Harch PG. Hyperbaric oxygen therapy for post-concussion syndrome: contradictory conclusions from a study mischaracterized as sham-controlled. *J Neurotrauma.* 2013;30(23):1995-1999.	E7
46	Harch PG. Department of Defense trials for hyperbaric oxygen and TBI: issues of study design and questionable conclusions. *Undersea Hyperb Med.* 2013;40(5):469-470.	E7
47	Harch PG, Andrews SR, Fogarty EF, et al. A phase I study of low-pressure hyperbaric oxygen therapy for blast-induced post-concussion syndrome and post-traumatic stress disorder. *J Neurotrauma.* 2012;29(1):168-185.	E4
48	Harch PG, Andrews SR, Fogarty EF, Lucarini J, Van Meter KW. Case control study: hyperbaric oxygen treatment of mild traumatic brain injury persistent post-concussion syndrome and post-traumatic stress disorder. *Medical gas research.* 2017;7(3):156-174.	E6
49	Hart BB, Weaver LK, Gupta A, et al. Hyperbaric oxygen for mTBI-associated PCS and PTSD: Pooled analysis of results from Department of Defense and other published studies. *Undersea Hyperb Med.* 2019;46(3):353-383.	E8
50	Hart BB, Weaver LK, Wilson SH, Lindblad AS, Churchill S, Deru K. Executive summary: Secondary analyses of DoD-sponsored studies examining hyperbaric oxygen for persistent post-concussive symptoms after mild traumatic brain injury. *Undersea Hyperb Med.* 2019;46(3):221-226.	E7

#	Citation	Exclude reason
51	Hawkins JR, Gonzalez KE, Heumann KJ. The Effectiveness of Hyperbaric Oxygen Therapy as a Treatment for Postconcussion Symptoms. *J Sport Rehabil.* 2017;26(3):290-294.	E8
52	Hexdall E, Brave R, Kraft K, Siewers J. Diving deep into hyperbaric oxygen therapy. *Nursing.* 2016;46(10):28.	E7
53	Hoge CW, Jonas WB. Hyperbaric Oxygen Treatment for Persistent Postconcussion Symptoms--Reply. *JAMA Internal Medicine.* 2015;175(7):1241.	E7
54	Hoge CW, Jonas WB. The ritual of hyperbaric oxygen and lessons for the treatment of persistent postconcussion symptoms in military personnel. *JAMA Internal Medicine.* 2015;175(1):53-54.	E7
55	Holbach K, Wassmann H, Kolberg T. Improved reversibility of the traumatic midbrain syndrome using hyperbaric oxygen. *Acta Neurochir (Wien).* 1974;30(3-4):247-256.	E9*
56	Hooker JS. Hyperbaric Oxygen Therapy: Using Evidence-Based Medicine to Heal Injured Brain Tissue. *N C Med J.* 2016;77(1):69-70.	E7
57	Hu Q, Manaenko A, Guo Z, Huang L, Tang J, Zhang JH. Hyperbaric oxygen therapy for post concussion symptoms: issues may affect the results. *Medical gas research.* 2015;5:10.	E7
58	Hu Q, Manaenko A, Xu T, Guo Z, Tang J, Zhang JH. Hyperbaric oxygen therapy for traumatic brain injury: bench-to-bedside. *Medical gas research.* 2016;6(2):102-110.	E7
59	Indiana State Department of Health. The implementation of a program for the specific treatment of veterans with traumatic brain injury or posttraumatic stress disorder as mandated by SEA 180. 2014.	E7
60	Karam C, Griggs RC. "Hyperbaric oxygen: B-level evidence in mild traumatic brain injury clinical trials": Editors' note. *Neurology.* 2017;89(7):750.	E10
61	Klugar M, Nytra I, Bocková S, Klugarová J, Kelnarová Z, Marecková J. The effectiveness of hyperbaric oxygen therapy on mortality in adults with craniotrauma: a systematic review protocol. *JBI Database of Systematic Reviews and Implementation Reports.* 2014;12(12):54-66.	E7
62	Kohlenberg A, Mody K. Hyperbaric oxygen for post-concussion symptoms secondary to mild traumatic brain injury. *Clin J Sport Med.*24(2):193.	E7
63	Korley F RGGBMRSRBW. The design of the hyperbaric oxygen brain injury treatment (Hobit) trial. *Journal of neurotrauma.*34(13):A59-A60.	E7
64	Lindblad As WPAWLKMCWSHKMAVZD. Eyetracker outcomes in a randomized trial of hyperbaric oxygen or sham in participants with persistent post-concussive symptoms. *Investigative ophthalmology & visual science.* 2018;59(9).	E10
65	Mao J, Sun Z, Xiang Y. Observation of curative effects of hyperbaric oxygen for treatment on severe craniocerebral injury. *J Clin Neurol.* 2010;23(5):386-388.	E9*
66	Marois P, Mukherjee A, Ballaz L. Hyperbaric Oxygen Treatment for Persistent Postconcussion Symptoms--A Placebo Effect? *JAMA Internal Medicine.* 2015;175(7):1239-1240.	E7
67	Mathieu D, Marroni A, Kot J. Tenth European Consensus Conference on Hyperbaric Medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. *Diving Hyperb Med.* 2017;47(1):24-32.	E9

#	Citation	Exclude reason
68	McCrary BF, Weaver L, Marrs K, et al. Hyperbaric oxygen (HBO2) for post-concussive syndrome/chronic TBI--product summary. *Undersea Hyperb Med.* 2013;40(5):443-467.	E7
69	McDonagh M, Helfand M, Carson S, Russman BS. Hyperbaric oxygen therapy for traumatic brain injury: a systematic review of the evidence. *Archives of Physical Medicine & Rehabilitation.* 2004;85(7):1198-1204.	E8
70	McMonnies CW. Hyperbaric oxygen therapy and the possibility of ocular complications or contraindications. *Clinical and Experimental Optometry.* 2015;98(2):122-125.	E4
71	Meehan A, Hebert D, Deru K, Weaver LK. Longitudinal study of hyperbaric oxygen intervention on balance and affective symptoms in military service members with persistent post-concussive symptoms. *Journal of Vestibular Research.* 2019;29(4):205-219.	E6
72	Meyer G, Hubbard M, Vonderhaar K, et al. Headache prevalence 30 years after severe traumatic brain injury. *Brain injury.* 2017;Conference: 12th world congress on brain injury of the international brain injury association. United states. 31(6-7):941.	E4
73	Miller RS, Weaver LK, Brenner LA. Hyperbaric Oxygen Treatment for Persistent Postconcussion Symptoms--Reply. *JAMA Internal Medicine.* 2015;175(7):1240-1241	E7
74	Mitchell SJ, Bennett MH. Unestablished indications for hyperbaric oxygen therapy. *Diving Hyperb Med.* 2014;44(4):228-234.	E7
75	Mozayeni BR, Duncan W, Zant E, Love TL, Beckman RL, Stoller KP. The National Brain Injury Rescue and Rehabilitation Study - a multicenter observational study of hyperbaric oxygen for mild traumatic brain injury with post-concussive symptoms. *Medical gas research.* 2019;9(1):1-12.	E6
76	Ren H, Wang W, Ge Z, Zhang J. Clinical, brain electric earth map, endothelin and transcranial ultrasonic Doppler findings after hyperbaric oxygen treatment for severe brain injury. *Chinese Medical Journal.* 2001;114(4):387-390.	E4
77	Report to Congress on the Use of Hyperbaric Oxygen for Medical Care and Research in Response to H.R. 3326, the Department of Defense Appropriations Act for Fiscal Year 2010. 2011.	E7
78	Rockswold SB, Rockswold GL, Zaun DA, et al. A prospective, randomized clinical trial to compare the effect of hyperbaric to normobaric hyperoxia on cerebral metabolism, intracranial pressure, and oxygen toxicity in severe traumatic brain injury. *Journal of Neurosurgery.* 2010;112(5):1080-1094.	E4*
79	Sawyer Q, Vesci B, McLeod TC. Physical Activity and Intermittent Postconcussion Symptoms After a Period of Symptom-Limited Physical and Cognitive Rest. *J Athlet Train.* 2016;51(9):739-742.	E2
80	Schnurr PP, Hermann BA, Mott JM. Clinician's Trauma Update, December 2014. 2014;8:1-3.	E7
81	Shandley S, Wolf EG, Schubert-Kappan CM, et al. Increased circulating stem cells and better cognitive performance in traumatic brain injury subjects following hyperbaric oxygen therapy. *Undersea Hyperb Med.* 2017;44(3):257-269.	E4
82	Shytle RD, Eve DJ, Kim SH, Spiegel A, Sanberg PR, Borlongan CV. Retrospective Case Series of Traumatic Brain Injury and Post-Traumatic Stress Disorder Treated with Hyperbaric Oxygen Therapy. *Cell Transplantation.* 2019;28(7):885-892.	E6

#	Citation	Exclude reason
83	Skipper LD, Churchill S, Wilson SH, Deru K, Labutta RJ, Hart BB. Hyperbaric oxygen for persistent post-concussive symptoms: long-term follow-up. *Undersea Hyperb Med.* 2016;43(5):601-613.	E4
84	Stoller KP. All the right moves: the need for the timely use of hyperbaric oxygen therapy for treating TBI/CTE/PTSD. *Medical gas research.* 2015;5:7.	E7
85	Tal S, Hadanny A, Berkovitz N, Sasson E, Ben-Jacob E, Efrati S. Hyperbaric oxygen may induce angiogenesis in patients suffering from prolonged post-concussion syndrome due to traumatic brain injury. *Restor Neurol Neurosci.* 2015;33(6):943-951.	E4
86	Tal S, Hadanny A, Sasson E, Suzin G, Efrati S. Hyperbaric Oxygen Therapy Can Induce Angiogenesis and Regeneration of Nerve Fibers in Traumatic Brain Injury Patients. Front Hum Neurosci. 2017;11:508.	E4
87	The American Legion TBI/PTSD Ad Hoc Committee. The War Within: Treatment of Traumatic Brain Injury and Post Traumatic Stress Disorder. 2013.	E7
88	TreatNow. HBOT Research and Science. 2017.	E7
89	Tsutsumi Y, Tsutsumi I, Tsujimoto Y, et al. Hyperbaric oxygen therapy for persistent post-concussion syndrome following mild traumatic brain injury. Cochrane Database of Systematic Reviews. 2017(7).	E7
90	United States Government Accountability Office. Research on Hyperbaric Oxygen Therapy to Treat Traumatic Brain Injury and Post-Traumatic Stress Disorder. 2015.	E7
91	VanDerMeulen MD. Treatment of traumatic brain injuries: A meta-analysis comparing low level light (Laser)therapy and hyperbaric oxygen therapy. *Dissertation Abstracts International: Section B: The Sciences and Engineering.* 2019;80(3-B(E).	E8
92	Veterans Affairs/Department of Defense. Clinical Practice Guidelines for The Management of Concussion-mild Traumatic Brain Injury (mTBI). 2016.	E7
93	Veterans Affairs/Department of Defense. Clinical Practice Guideline for The Management of Posttraumatic Stress Disorder and Acute Stress Disorder. 2017.	E7
94	Walker JM, Mulatya C, Hebert D, Wilson SH, Lindblad AS, Weaver LK. Sleep assessment in a randomized trial of hyperbaric oxygen in U.S. service members with post concussive mild traumatic brain injury compared to normal controls. *Sleep Medicine.* 2018;51:66-79.	E4
95	Wang Y, Chen D, Chen G. Hyperbaric oxygen therapy applied research in traumatic brain injury: from mechanisms to clinical investigation. *Medical gas research.* 2014;4:18.	E7
96	Wang F, Wang Y, Sun T, Yu HL. Hyperbaric oxygen therapy for the treatment of traumatic brain injury: a meta-analysis. *Neurological Sciences.* 2016;37(5):693-701.	E8*
97	Weaver LK, Chhoeu A, Lindblad AS, Churchill S, Deru K, Wilson SH. Executive summary: The Brain Injury and Mechanism of Action of Hyperbaric Oxygen for Persistent Post-Concussive Symptoms after Mild Traumatic Brain Injury (mTBI) (BIMA) Study. *Undersea Hyperb Med.* 2016;43(5):485-489.	E7
98	Weaver LK, Chhoeu A, Lindblad AS, Churchill S, Wilson SH. Hyperbaric oxygen for mild traumatic brain injury: Design and baseline summary. *Undersea Hyperb Med.* 2016;43(5):491-509.	E7

#	Citation	Exclude reason
99	Weaver LK, Cifu D, Hart B, Wolf G, Miller S. Hyperbaric oxygen for post-concussion syndrome: design of Department of Defense clinical trials. *Undersea Hyperb Med.* 2012;39(4):807-814.	E7
100	Williams CS, Spitz MC, Foley JF, Weaver LK, Lindblad AS, Wierzbicki MR. Baseline EEG abnormalities in mild traumatic brain injury from the BIMA study. *Undersea Hyperb Med.* 2016;43(5):521-530.	E4
101	Williams CS, Weaver LK, Lindblad AS, Kumar S, Langford DR. Baseline neurological evaluations in a hyperbaric trial of post-concussive syndrome. *Undersea Hyperb Med.* 2016;43(5):511-519.	E4
102	Wilson SH, Weaver LK, Lindblad AS. Neuropsychological assessments in a hyperbaric trial of post-concussive symptoms. *Undersea Hyperb Med.* 2016;43(5):585-599.	E4
103	Xu L, Li B, Yang C, Li C, Peng Y. Clinical research on postoperative efficacy and related factors of early simulation hyperbaric oxygen therapy for severe craniocerebral injury. *Pak.* 2016;29(1 Suppl):273-280	E4

*Included in 2018 ESP report

APPENDIX E: EVIDENCE TABLES

CHARACTERISTICS OF INCLUDED PRIMARY STUDIES

Author Year N	Study design Setting Follow-up	Population Patient Characteristics	TBI severity, # TBIs, time since TBI	% with PTSD diagnosis or meeting criteria for baseline PTSD score	HBOT Characteristics	Comparator
Artru, 1976[8] N=60	RCT Neurological ICU 12 months	Patients with head injuries in a coma in a neurological ICU Age: 30 yrs %male: NR %white: NR	Severity of coma: 9.49 (Jouvet scale)	NR	2.5 ATA 10 daily 1.5-hour sessions, 4 days no session, repeated until patient recovered consciousness or died	Standard care (details NR)
BIMA Weaver, 2018[9] Hart, 2019[10] Weaver, 2019[11] Churchill, 2019[12] N=71	RCT Military Outpatient 12 months (24-36 in 42 patients)	Military personnel with persistent post-concussive symptoms 3 to 5 years after mild TBI Age: 32.8 yrs %male: 98.6 %white: NR	mild TBI Mean 3.6 mild TBIs (lifetime), 26 months post most recent TBI	49%	1.5 ATA 40 1-hour sessions (> 99% oxygen) over 12 weeks	Sham HBOT at 1.2 ATA, room air
Boussi-Gross, 2013[13] N=90 (56 analyzed)	Randomized Crossover Trial Outpatient Hyperbaric Chamber 2 months	mTBI patients 1-6 years after injury with post-concussion syndrome Age: 44 yrs %male: 43 %white: NR	mild TBI 33-month average time since mild TBI	NR	1.5 ATA 40 1-hour sessions (100% oxygen), 5 days/week	No treatment

Author Year N	Study design Setting Follow-up	Population Patient Characteristics	TBI severity, # TBIs, time since TBI	% with PTSD diagnosis or meeting criteria for baseline PTSD score	HBOT Characteristics	Comparator
Cifu, 2014[14] Cifu, 2014[15] Walker, 2014[16] N=61	RCT Military Outpatient 3 months	Military personnel with mTBI and post-concussive symptoms for at least 3 months Age: 23.2 yrs %male: 100 %white: 78.3	mild TBI 8.5 month average since most recent mTBI, all deployment-related mTBI caused by blasts	36%	2.0 ATA 40 1-hour sessions (75% (1.5 ATA equivalent) or 100% oxygen) over 10 weeks	2.0 ATA, 10.5% oxygen (1.0 ATA equivalent, known as sham air)
HOPPS Miller, 2015[17] Weaver, 2019[11] Churchill, 2019[12] N=72	RCT Military Outpatient 10 weeks	Military servicemembers with post-concussive symptoms for at least 4 months, most recent was at least 4 months before randomization Age: 31.4 yrs %male: 96 %white: NR	mild TBI Mean 3 mTBIs (lifetime), average 23 months since last TBI	65%	1.5 ATA 40 1-hour sessions (100% oxygen) over 10 weeks	1.2 ATA or standard post-concussive care only
Harch, 2020[18] N=63	Randomized Crossover Trial Outpatient hyperbaric center 2 months	Patients with 1 or more blunt or blast TBIs at least 6 months prior with post-concussive symptoms Age: 42.6 %male: 45.1 %white: 92	mild TBI Mean 3.8 mTBIs at least 6 months since last TBI	0% clinical PTSD (CAPS) 61% PCL >=50	150 kPa 40 1-hour sessions, 5 days/week	No treatment
Lin, 2008[19] N=44	RCT Outpatient hyperbaric center 6 months	Hospitalized patients with moderate to severe TBI Age: 66% aged 25-64 %male: 86.3 %white: NR	Mean GCS baseline: 8.0 average time since injury: 27.5 days	NR	2.0 ATA 20 2-hour sessions (100% oxygen), once a day for 20 days over 4 weeks	Standard neurosurgical therapy

Author Year N	Study design Setting Follow-up	Population Patient Characteristics	TBI severity, # TBIs, time since TBI	% with PTSD diagnosis or meeting criteria for baseline PTSD score	HBOT Characteristics	Comparator
Ren, 2001[20] N=55	RCT Inpatient 6 months	Hospitalized patients with severe brain injury Age: 34.9 yrs %male: 76.4 %white: NR	Mean GCS baseline: 5.2	NR	0.25 mPa 30-40 40-60-minute sessions (100% oxygen), delivered in 10 session increments/4 days	Dehydrating, cortical steroid and antibiotic therapy
Rockswold, 1985[21] N=30	RCT Inpatient 18 months	Hospitalized, severely brain-injured patients Age: NR %male: NR %white: NR	All ppts had GCS<10	NR	1.5 ATA 1-hour sessions (100% oxygen) every 4-8 hours for 2 weeks until patient was brain dead or awake	Standard intensive neurosurgical treatment
Rockswold, 1992[22] N=168	RCT Inpatient 12 months	Hospitalized, severely brain-injured patients Age: 32.5 %male: 74 %white: NR	Mean GCS baseline: 6.2	NR	1.5 ATA 1-hour sessions (100% oxygen) every 8 hours for 2 weeks until patient was brain dead or awake	Standard intensive neurosurgical treatment
Rockswold 2013[23] N=42	RCT Inpatient 6 months	Hospitalized patients with severe TBI Age: 35 %male: 72.7 %white: NR	Mean GCS baseline: 5.7	NR	1.5 ATA 1-hour sessions (100% oxygen) followed by 1.0 ATA every 24 hours for 3 days	Standard intensive neurosurgical treatment
Shi, 2003[24] N=320	RCT NR 18 months	Hospitalized patients with post brain injury neural status Age: 38.5 %male: 67.2 %white: NR	76.9% headache, dizziness, poor memory, and poor concentration, 12.8% epilepsy, 10.3% hydrocephalus	NR	0.1 mPa 10 90-min sessions (96% oxygen) over 10 days	Medication therapy

Author Year N	Study design Setting Follow-up	Population Patient Characteristics	TBI severity, # TBIs, time since TBI	% with PTSD diagnosis or meeting criteria for baseline PTSD score	HBOT Characteristics	Comparator
Wolf, 2012[25] Wolf, 2012[26] Wolf, 2015[27] N=50	RCT Military outpatient 14 weeks	Military servicemembers with post-concussive symptoms and at least one combat-related mTBI. Age: 28.3 %male: 96 %white: NR	mild TBI Mean 3.4 concussions prior to injury. 66% ppts had TBIs from IED, 16% from head trauma, and 18% from both.	NR	1.3 ATA (sham)	Post-concussive symptoms (ImPACT, PCL-M).
Xie, 2007[28] N=60	RCT Inpatient NR	Hospitalized patients with craniocerebral injury Age: 26 %male: 62 %white: NR	Baseline GCS = 8.2	NR	0.2 - 0.25 mPa 10 70-80 min sessions, once a day for 10 days	Standard neurosurgical therapy

Abbreviations. ATA=Atmospheres absolute, CAPS=Clinician Administered PTSD Scale, GCSG=Glasgow Coma Scale, HBOT=Hyperbaric oxygen therapy, ICU=Intensive care unit, imPACT=Immediate post-concussive assessment, kPA=Kilopascal pressure unit, mTBI=Mild traumatic brain injury, mPa=Megapascal pressure unit, NR=Not reported, PCL-M=PTSD Checklist – Military Version, Ppts=Participants, PTSD=Post traumatic stress disorder, RCT=Randomized controlled trial, TBI=Traumatic Brain Injury.

OUTCOME DATA OF INCLUDED PRIMARY STUDIES

A data table of effect estimates used in meta-analyses is available upon request by contacting ESP.CC@va.gov.

QUALITY ASSESSMENT OF INCLUDED PRIMARY STUDIES

Author Year	Risk of bias from randomization process	Risk of bias from deviation from intended interventions (assignment)	Risk of bias from deviation from intended interventions (adherence)	Risk of bias from missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall bias (High, Low, Unclear)
Artru 1976[8]	Unclear Random sequence and allocation concealment method not described. Age, severity of coma, and "therapeutic measures" similar between groups but % with acute subdural hematoma was different. Other differences between groups not reported.	Unclear Participants unconscious. Unclear if there were deviations in assignment or intervention protocol.	High Participants unconscious. Time lags to start of intervention resulted in only 17 of 31 pts having 4 sessions within first 7 days. 11 cases discontinued tx. due to intolerance. 7 pts that were categorized as not operated on were eventually operated on, but rates similar between HBOT and control groups.	Low Appears to be outcome data for all participants.	Unclear Outcome assessors likely aware of intervention assignment. Mortality and length of coma unlikely to be affected by knowledge of intervention, unclear how "quality of recovery" was measured.	Unclear Protocol not readily accessible.	High
BIMA Weaver, 2018[9] Hart, 2019[10] Weaver, 2019[11] Churchill, 2019[12]	Low Computer-generated randomization. Some differences between groups (age, anger control, diffuse/ traumatic axonal injury) at baseline. Adjustment for baseline differences in analyses.	Unclear Participants blinded to intervention status. Unclear if there were deviations in assignment or intervention protocol.	Low Participants blinded to interventions status. 81% of HBOT and 86% of sham ppts completed 40 sessions. Medication, supplement, and therapy use similar between groups.	Low 36/36 HBOT group completed 12-month visit and 32/35 sham completed 12-month visit.	Low Outcome assessors were blinded. Outcomes self-reported, but participants blinded.	Low Other outcomes besides post-concussive symptoms not listed in protocol. However, no apparent deviations.	Low

Author Year	Risk of bias from randomization process	Risk of bias from deviation from intended interventions (assignment)	Risk of bias from deviation from intended interventions (adherence)	Risk of bias from missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall bias (High, Low, Unclear)
Boussi-Gross, 2013[13]	Unclear Random sequence and allocation concealment method not described. Only 1 significant difference between groups (education).	Unclear Participants aware of intervention status. Unclear if there were deviations in assignment or intervention protocol.	Unclear Participants aware of intervention status. 4 ppts excluded due to inconsistent use of medications (2 in each group). 4 patients dropped out and did not complete intervention protocol (1 crossover, 3 treatment).	High Only 24/45 crossover and 32/45 HBOT ppts completed study. 19 patients withdrew consent prior to intervention (13 crossover, 6 treatment). 11 (out of 71 who started treatment) patients were excluded from analysis (7 crossover, 4 treatment).	Unclear. Outcome assessors likely aware of intervention assignment, and neurological test outcomes could have been influenced by knowledge of intervention.	Low Only "neurological evaluation" listed in protocol and there is no mention of quality of life. However, no apparent deviations.	High
Cifu, 2014[14] Cifu, 2014[15] Walker, 2014[16]	Low Computer-generated randomization. No differences between groups at baseline.	Low Participants blinded to intervention status. 100% received intervention as assigned.	Low Participants blinded to intervention status. All participants received assigned intervention, 3 lost to follow-up. Unclear cointerventions.	Low 3/61 ppts lost to follow up.	Low Investigators and participants were blinded.	Low No deviations from protocol observed.	Low

Author Year	Risk of bias from randomization process	Risk of bias from deviation from intended interventions (assignment)	Risk of bias from deviation from intended interventions (adherence)	Risk of bias from missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall bias (High, Low, Unclear)
HOPPS Miller, 2015[17] Weaver, 2019[11] Churchill, 2019[12]	Unclear Random sequence and allocation concealment method not described. No baseline differences between groups.	Unclear Participants blinded to intervention status, although 1 group received usual care. Unclear if there were deviations in assignment or intervention protocol.	Low Participants blinded to intervention status, although 1 group received usual care. 7 pts discontinued (similar #s between groups). Concurrent interventions for PCS and PTSD similar between groups.	Low 8/72 lost to follow-up. Unclear handling of missing data.	Unclear Outcome assessors blinded to intervention group. Some self-report outcomes could be influenced by knowledge of intervention for the usual care group.	Low for post-concussive symptoms. High for composite measure of HBOT effectiveness (Weaver 2019)	Low
Harch, 2020[18]	Low Computer generated random sequence generation. Allocation concealment method not described. No baseline differences between treatment and control groups.	Unclear Participants aware of intervention status. 6/31 HBOT and 2/29 control did not receive allocated intervention.	Unclear Participants aware of intervention status. 4/63 did not complete all 40 sessions. 10 dropouts after randomization (8 treatment, 2 control) Unclear matching of dropouts to flow diagram.	Unclear 7/63 lost to follow-up, #s similar between groups. 72-83% included in analysis. 50/60 included in post-HBOT analysis and 43/60 completed 2-month follow-up.	Unclear Outcome assessor blinded to intervention group, but some outcomes were self-report.	Low Depression and anxiety measurements not reported in Clinicaltrials.gov protocol. However, no apparent deviations.	Unclear

Author Year	Risk of bias from randomization process	Risk of bias from deviation from intended interventions (assignment)	Risk of bias from deviation from intended interventions (adherence)	Risk of bias from missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall bias (High, Low, Unclear)
Lin, 2008[19]	Unclear Random sequence and allocation concealment method not described. Only intervention group was randomized, control group was selected to match randomized group. No differences between groups at baseline.	Unclear Participants aware of intervention status. Participants apparently received more HBOT sessions than intended (average 24.4 sessions, intended to be 20 sessions)	Unclear Participants aware of intervention status. More control ppts (20/22) than intervention ppts (16/22) appear to have had surgery.	High Any ppts with complications during HBOT and their corresponding controls were excluded. 44/62 patients had complete data available for analysis.	Unclear Outcome assessors aware of intervention assignment. GOS assessment may be influenced by knowledge of treatment.	Unclear Protocol not readily accessible.	High
Ren, 2001[20]	Unclear Random sequence and allocation concealment method not described. No baseline differences between groups.	Unclear Participants aware of intervention status. Unclear if there were deviations in assignment or intervention protocol.	Unclear Participants aware of intervention status. Unclear co-interventions. States "all participants had 3-4 courses of therapy"	Low Appears to be outcome data for all participants.	Unclear Outcome assessors likely aware of intervention assignment. GCS assessment may be influenced by knowledge of treatment.	Unclear Protocol not readily accessible.	Unclear

Author Year	Risk of bias from randomization process	Risk of bias from deviation from intended interventions (assignment)	Risk of bias from deviation from intended interventions (adherence)	Risk of bias from missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall bias (High, Low, Unclear)
Rockswold, 1985[21]	Unclear Random sequence and allocation concealment method not described. No assessment of baseline differences between groups.	Unclear Participants unconscious. Unclear if there were deviations in assignment or intervention protocol.	Low Participants unconscious. Appears all participants randomized to HBOT received treatment and were managed similarly besides administration of HBOT.	Low Appears to be outcome data for all participants who survived.	Low GCS outcome assessors blinded to treatment. Mortality objective outcome.	Unclear Protocol not readily accessible.	Unclear
Rockswold, 1992[22]	Unclear Random sequence and allocation concealment method not described. Groups similar at baseline.	Unclear Participants aware of intervention status. 24/84 HBOT participants had deviations from intervention protocol. 4/84 HBOT participants did not receive therapy.	Unclear Participants aware of intervention status. Unclear co-interventions. 10 pts discontinued HBOT per request by family members.	Low 2/168 participants lost to follow-up (both in control group)	Low GOS outcome assessors blinded to treatment. Mortality objective outcome.	Unclear Protocol not readily accessible.	Unclear

Author Year	Risk of bias from randomization process	Risk of bias from deviation from intended interventions (assignment)	Risk of bias from deviation from intended interventions (adherence)	Risk of bias from missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall bias (High, Low, Unclear)
Rockswold, 2013[23]	Unclear Random sequence and allocation concealment method not described. Groups similar at baseline.	Unclear Participants aware of intervention status. Unclear if there were deviations in assignment or intervention protocol.	Unclear Participants aware of intervention status. Similar cointerventions: 1 intervention vs 2 control group ppts received surgery after randomization. Unclear adherence.	Low 2/42 participants lost to follow-up (1 in each control/intervention)	Low GOS outcome assessors blinded to treatment. Mortality objective outcome	Low GOS and mortality not listed as outcomes in CT.gov protocol, but no apparent deviations.	Unclear
Shi, 2003[24]	Unclear Random sequence and allocation concealment method not described. No significant difference between groups in terms of types of brain injury (intracranial hematomas, brain contusions, concussions), other differences not assessed.	Unclear Participants aware of intervention status. Unclear if there were deviations in assignment or intervention protocol.	Unclear Participants aware of intervention status. Unclear co-interventions and adherence	Low All patients followed for 6-18 months.	High Unclear blinding of outcome assessors. Unclear how "resolution of symptoms" was measured.	Unclear Protocol not readily accessible.	High

Author Year	Risk of bias from randomization process	Risk of bias from deviation from intended interventions (assignment)	Risk of bias from deviation from intended interventions (adherence)	Risk of bias from missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall bias (High, Low, Unclear)
Wolf, 2012[25] Wolf, 2012[26] Wolf, 2015[27]	Low Computer-generated randomization. No differences in groups at baseline except greater nausea in sham group.	Unclear Participants blinded to intervention status. Blind assessed at the end of the study. Unclear if there were deviations in assignment or intervention protocol.	Low Participants blinded to interventions status. All but 2 participants completed study.	Low 1 withdrawal from each group.	Low Outcome assessors blinded. Outcome self-reported, but participants blinded.	Low No deviations from protocol observed.	Low
Xie, 2007[28]	Unclear Random sequence and allocation concealment method not described. No f baseline differences between groups in sex, age, disease structure, and grades of cerebral injury.	Unclear Participants aware of intervention status. Unclear if there were deviations in assignment or intervention protocol.	Unclear Participants aware of intervention status. Unclear co-interventions and adherence.	Low Outcome data available for all participants.	Unclear Unclear blinding of outcome assessors. Minimal info on how GCS data was collected.	Unclear Protocol not readily accessible.	Unclear

Abbreviations. BIMA=Brain Injury and Mechanisms of Action of HBO2 for persistent post-concussive symptoms after mild TBI study, GCS=Glasgow coma scale, GOS=Glasgow outcome scale, HBOT=Hyperbaric oxygen therapy, Ppts=Participants, Pts=Patients, PTSD=Post traumatic stress disorder, Tx=Treatment.

STRENGTH OF EVIDENCE

Mild TBI

Outcome	Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Summary of evidence
PTSD Symptoms (PCL)	Compared to sham HBOT: 4 studies [9-12,14-16] (N=254)	Low RoB	Direct	Inconsistent	Imprecise	Not detected	Low SOE: HBOT does not lead to consistent or durable improvements in PTSD symptoms among patients with mTBI (MD = 0.61, 95% CI [-7.75, 8.96], p = 0.38). Confidence is limited by imprecise and inconsistent findings among studies.
	Compared to no treatment/ standard care: 2 studies[11,12,17,18] (N=135)	Low to unclear RoB	Direct	Consistent	Imprecise	Not detected	Low SOE: HBOT led to greater short-term improvement in PTSD symptoms than no treatment or standard care control groups, but pooled effects were nonsignificant (MD = -7.41, 95% [-59.22, 44.41], p = 0.33). Confidence is limited by methodological limitations and imprecision.
Post-concussive symptoms (RPQ/NSI)	Compared to sham HBOT: 3 studies [9,11,12,9,10,12,14-17] (N=204)	Low RoB	Direct	Inconsistent	Imprecise	Not detected	Low SOE: HBOT does not lead to consistent or durable improvements in post-concussion symptoms among patients with mTBI (g = -0.09, 95% CI [-0.44, 0.26], p = 0.83). Confidence is limited by imprecise and inconsistent findings among studies.
	Compared to no treatment: 2 studies[11,12,17,18] (N=135)	Low to unclear RoB	Direct	Unclear	Imprecise	Not detected	Low SOE: HBOT led to greater short-term improvement (2 to 4 months) in post-concussion symptoms than no treatment, but pooled effects were nonsignificant (g = -1.51, 95% CI [-18.96, 15.94], p = 0.45). Confidence is limited by methodological limitations and imprecision.

Abbreviations. HBOT=Hyperbaric oxygen therapy NSI=Neurobehavioral Symptom Inventory, PCL=PTSD checklist, PTSD=Post traumatic stress disorder, RoB=Risk of bias, RPQ= Rivermead post-concussive questionnaire, SOE=Strength of evidence.

Moderate to Severe TBI

Outcome	Studies*	Study limitations	Directness	Consistency	Precision	Reporting bias	Summary of evidence
Mortality	4 studies[8,21-23] (N=300)	Unclear to High RoB	Direct	Inconsistent	Unknown	Not detected	Low SOE: HBOT may reduce mortality compared to standard treatment at 6 months to 1 year. Confidence limited by mostly small studies with unclear to high RoB and inconsistent findings.
Glasgow coma scale	3 studies[19,20,28] (N=159)	Unclear to High RoB	Direct	Consistent	Unknown	Not detected	Low SOE: HBOT may improve GCS compared to standard treatment post-treatment. Confidence limited by mostly small studies with unclear to high RoB.
Glasgow outcomes score	5 studies[19-23] (N=339)	Unclear RoB	Direct	Inconsistent	Unknown	Not detected	Low SOE: Evidence is conflicted on whether HBOT improves GOS compared to standard treatment at 3 to 12 months. Confidence limited by mostly small studies with unclear to high RoB and inconsistent findings.

*All compared to standard neurological intensive care
Abbreviations. HBOT=Hyperbaric oxygen therapy, RoB=Risk of bias, SOE=Strength of evidence.

Unclear TBI Severity

Outcome	Studies	Study limitations	Directness	Consistency	Precision	Reporting bias	Summary of Evidence
Symptom Improvement	Shi, 2003[24] (N=320)	High RoB	Unclear	Unclear	Unknown	Not detected	Insufficient SOE: It is uncertain whether or not HBOT improves symptoms in patients with TBI (severity unknown). Confidence limited by a single study with high risk of bias and unclear method to measure symptoms.

Abbreviations. GOS=Glasgow outcome scale, HBOT=Hyperbaric oxygen therapy, RoB=Risk of bias, SOE=Strength of evidence, TBI=Traumatic brain injury.

APPENDIX F: RESEARCH IN PROGRESS

Status	Study Title	Study Design	Information Resources (Registry #; citation(s) for published protocols; links to project websites)
Active, not recruiting	Hyperbaric Treatment of Traumatic Brain Injury (TBI)	RCT	Barry Miskin, MD, Jupiter Medical Center NCT01847755
Unknown	Hyperbaric Oxygen Therapy and SPECT Brain Imaging in Traumatic Brain Injury	RCT	Paul G. Harch, MD, Louisiana State University Health Sciences Center in New Orleans NCT00594503
Active, recruiting	Hyperbaric Oxygen Brain Injury Treatment Trial (HOBIT)	RCT	Minneapolis Medical Research Foundation NCT02407028
Terminated	Hyperbaric Oxygen Therapy in Chronic Traumatic Brain Injury or Post-Traumatic Stress Disorder (NBIRR-1)	RCT	International Hyperbaric Medical Foundation NCT01105962 *(new regulatory requirements will require funding for restart as a new study)*

APPENDIX G: TABLE OF MEASURES

PTSD

Acronym	Tool Name	Source
BDI	Beck Depression Inventory	2018 AHRQ PTSD
CAPS	Clinician Administered PTSD	2018 AHRQ PTSD SR Amos 2014 Sin 2017 Suomi 2019
CIDI	Comprehensive International Diagnostic Interview	Amos 2014
DTS	Davidson Trauma Scale	2018 AHRQ PTSD SR
GAF	Global Assessment of Functioning	2018 AHRQ PTSD SR
HADS	Hospital Anxiety and Depression Scale	2018 AHRQ PTSD SR
HAM-A or HAS	Hamilton Anxiety Scale	2018 AHRQ PTSD SR
HAM-D	Hamilton Depression Scale	2018 AHRQ PTSD SR
IES	Impact of Event Scale	2018 AHRQ PTSD SR
MADRS	Montgomery-Asberg Depression Rating Scale	2018 AHRQ PTSD SR
MISS or M-PTSD	Mississippi Scale for Combat-Related PTSD	2018 AHRQ PTSD SR
MPSS-SR	Modified PTSD Symptom Scale	2018 AHRQ PTSD SR
PCL	PTSD Checklist	2017 VA/DoD PTSD and acute stress disorder guideline 2018 AHRQ PTSD SR Suomi 2019
PC-PTSD	PC-PTSD Screen	2017 VA/DoD PTSD and acute stress disorder guideline
PSS-I	PTSD Symptom Scale Interview	2018 AHRQ PTSD SR Suomi 2019 2019
PSS-SR	PTSD Symptom Scale Self-Report Version	2018 AHRQ PTSD SR
PTDS or PDS	Posttraumatic Diagnostic Scale	2018 AHRQ PTSD SR
PTSD-I	PTSD Interview	2018 AHRQ PTSD SR
PTSS-10Q-1	PTSD 10-Questions Inventory	Amos 2014
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form	2018 AHRQ PTSD SR
SCID	Structured Clinical Interview PTSD Module	2018 AHRQ PTSD SR Amos 2014
SCL-90-R	Symptom Checklist-90-Revised	2018 AHRQ PTSD SR
SDS	Sheehan Disability Scale	2018 AHRQ PTSD SR
SF-12	Medical Outcome Study Self-Report Form	2018 AHRQ PTSD SR
SF-36	36-Item Short Form Health Survey	2018 AHRQ PTSD SR
SI-PTSD or SIP	Structured Interview for PTSD	2018 AHRQ PTSD SR
SPRINT	Short PTSD Rating Interview	2018 AHRQ PTSD SR
STAI	State-Trait Anxiety Inventory	2018 AHRQ PTSD SR
TOP-8	Treatment-Outcome Post-Traumatic Stress Disorder Scale	2018 AHRQ PTSD SR
WAS	Work and Social Adjustment Scale	2018 AHRQ PTSD SR

TBI

Acronym	Tool Name	Source
ACE	Acute Concussion Evaluation	Ontario Neurotrauma Foundation, Guideline for Concussion/Mild Traumatic Brain Injury, 2018
ANAM	Automated Neuropsychological Assessment Metrics	VA/DoD Guideline Concussion-Mild Traumatic Brain Injury, 2016
A-WPTAS	Abbreviated Westmead Post-Traumatic Amnesia Scale	Ontario Neurotrauma Foundation, Guideline for Concussion/Mild Traumatic Brain Injury, 2018
AII	Auditory Immediate Index	CADTH 2007 Acetylcholinesterase
CNT	Cambridge Neuropsychological Test Automated Battery	Dougall 2015
CGI	Clinical Global Improvement	CADTH 2007 Acetylcholinesterase Dougall 2015
CIQ	Community Integration Questionnaire	Brasure 2012
CPT-II	Conner's Continuous Performance Test II	Dougall 2015
DRS	Disability Rating Scale	Willis 2015
DQ	Dysexecutive Questionnaire	CADTH 2007 Acetylcholinesterase
FIM	Functional Independence Measure	CADTH 2007 Acetylcholinesterase
GCS	Glasgow Coma Scale	Ontario Neurotrauma Foundation, Guideline for Concussion/Mild Traumatic Brain Injury, 2018 Alarcon 2017 CADTH 2007 Acetylcholinesterase
GOS	Glasgow Outcome Scale	CADTH 2007 Acetylcholinesterase Willis 2012 Martin Saborido 2019 Chen 2020
HADS	Hospital Anxiety and Depression Scale	CADTH 2007 Acetylcholinesterase Gertler 2015
HVLT	Hopkins Verbal Learning Test	CADTH 2007 Acetylcholinesterase Gertler 2015
ImPACT	Immediate Post-Concussion Assessment and Cognitive Testing	VA/DoD Guideline Concussion-Mild Traumatic Brain Injury, 2016 Dougall 2015
MPAI	Mayo-Portland Adaptability Index	Brasure 2012
NCAT	Neuro-Cognitive Assessment Tool	VA/DoD Guideline Concussion-Mild Traumatic Brain Injury, 2016
NSI	Neurobehavioral Symptom Inventory	Dougall 2015
PCSS	Post Concussion Symptom Scale	Ontario Neurotrauma Foundation, Guideline for Concussion/Mild Traumatic Brain Injury, 2018
RPQ	Rivermead Post Concussion Symptoms Questionnaire	Ontario Neurotrauma Foundation, Guideline for Concussion/Mild Traumatic Brain Injury, 2018
SF-12	Short Form 12 Item	Dougall 2015
TMT	Trail Making Test	Dougall 2015
WAIS	Wechsler Adult Intelligence Scale	Dougall 2015

APPENDIX H: PEER REVIEW DISPOSITION

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	2	Yes	None
2	3	Yes	None
3	4	Yes	None
4	5	Yes	None
5	6	Yes	None
6	8	*First Review* No - Using studies, such as Weaver, et al., (2018) that arrived at results using inappropriate statistics is a major flaw in this Evidence Brief. This reviewer strongly suggests that the ESP team goes back and review the statistical methods used by the authors before releasing the brief. In addition, there may be confusion regarding the use of HBOT for ACUTE severe TBI. Acute severe TBI and chronic mild TBI or PTSD are vastly different clinical situations, more separation should be provided in the brief and these clinical conditions should be discussed separately. *Second Review* Yes	Specific comments regarding Weaver et al. (2018) and HBOT for acute severe TBI are addressed in comments below.
7	9	Yes	None
Is there any indication of bias in our synthesis of the evidence?			
8	2	No	None
9	3	No	None
10	4	No	None
11	5	No	None
12	6	No	None
13	8	*First Review* Yes - Utilizing the Weaver et al. (2018) paper creates obvious bias since the paper utilizes dozens of comparisons without any corrections. The paper that Weaver et al (2018) cites, Tang, et al. (1993) has had limited citations and those that utilized the method	The report has been revised with a meta-analysis of included studies to overcome some issues with analyses in the individual studies. The conclusions, key findings, and summary of the

		from this paper did so a priori. In addition, the Boussi-Gross, et al. paper had no sham treatment and only a 2 month follow-up. Chronic effects of TBI can be both cognitive and noncognitive in nature. People having chronic impairments are very susceptible to believing, at least in the short-term, that an ineffective treatment is efficacious for various non-cognitive conditions. Non-sham treatment studies are bias when there is a TBI history and the treatment is open-labelled. Taking both these two papers together, it is biased to state that the first sentence on page 8, "Although findings indicate some effect of HBOT is likely..." *Second Review* No	findings have been revised with findings from the meta-analysis.
14	8	Not clear reason why the Brenner, et al. studies were ineligible publications when the Weaver et al (2018) with obvious statistical flaws is included and Boussi-Gross with the critical flaw of no placebo control were included. This type of selection of evidence gives the appearance of bias.	The Brenner, et al. study (HOPPS) was included as Miller, 2015 – which was the publication with full results from the trial – and is included in Table 1 and the meta-analysis.
15	9	No	None
Are there any published or unpublished studies that we may have overlooked?			
16	2	No	None
17	3	No	None
18	4	No	None
19	5	*First Review* Yes - See my review of the brief for details *Second Review* No	Addressed in comments below.
20	6	No	None
21	8	No	None
22	9	No	None
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.			
23	2	Page 4, line 50 FDA did not determine the indications, the UHMS did and that should be identified for clarity.	This has been revised for clarity.
24	2	Page 6, line 10 The office name has changed to VHA National Center for Healthcare Advancement and Partnerships and was	The requesting office name and purpose have been revised.

		formerly, Office of Community Engagement/Center for Compassionate Care Innovation. The review was requested in response to Section 702 of the Commander John Scott Hannon Veterans Mental Health Care Improvement Act of 2019. This is the same response for page 9, line 11	
25	2	Page 9, line 15 the findings will not be used to inform provision of HBOT. They will be submitted to the Committee on Veterans Affairs of the Senate and the Committee on Veterans Affairs of the House of Representatives a report on the results of the review. This review was not requested to inform future care, specifically.	The purpose and use of the review have been revised.
26	2	Page 33, line 28 I am the Nurse Executive for VHA National Center for Healthcare Advancement and Partnerships. OCE and CCI are former names that are no longer current.	The name of the office has been revised.
27	2	Page 33, line 33 Same organizational name for Christine Eickhoff.	The name of the office has been revised.
28	3	The background section does not accurately reflect the office that requested or identified a need to update the previous report.	The requesting office name has been revised.
29	3	pg 4 line 50: the report correctly describes that FDA "clears" devices for specific indications and the list of indications from Appendix A accurately reflects and references the list of indications maintained by UHMS. The reference to the UHMS list of indications should also be included in the narrative on page 4.	This has been corrected to refer to and cite UHMS as providing indications for HBOT use.
30	4	Page 1, lines 8 - 27, "Background." Page 4, lines 15 - 19 (same comments as from page 1) The requirement from congress related to S. 785, the Commander John Scott Hannon Veterans Mental Health Care Improvement Act of 2019. Specifically, the Act requires VA to "conduct of a systematic review of published research literature on off label use of hyperbaric oxygen therapy to treat post traumatic stress disorder and traumatic brain injury among veterans and nonveterans." findings will inform a study on the current program evaluation of HBOT for Veterans diagnosed with PTSD with or without TBI	The office name, purpose, and intended use of report have been revised in the executive summary and purpose sections of the report.
31	4	p. 4, line 15-16: see previous comments	The office name, purpose, and intended use of report have been revised in the executive summary and purpose sections of the report.
32	5	p. 1, line 8: I suggest that in mild TBI another key finding is the caveat that the same short-term improvement in symptoms is seen with the sham exposures used in the sham-controlled trials. I know	The key findings have been revised to reflect the findings from a newly added meta-analysis, which

		the authors make this point in the body of the brief, but I think it is a point worth adding in this summary (which is all many users will actually read). I interpret this as suggesting the observed improvements are likely due to a participation effect. I feel this is the key message we need to make interested parties aware of and sorting this out is our primary problem with evidence in this area. You make this point clearly in Table ES1, but I think it is important enough to emphasize here.	takes into account effects in both HBOT and control groups.
33	5	NOTE on 'sham'. One of the great controversies in this area is the characterization of the typical control exposures used here as 'sham'. I think it is an accurate term and use it myself frequently, but as you suggest later in the brief, the proponents of HBO for mTBI muddy the waters by claiming that any exposure in a chamber is potentially therapeutic. I suspect the authors are familiar with this argument. I therefore caution the liberal use of 'sham' in this document. I fear it may provoke criticism from the proponents of HBO that would distract from the important message of this brief. I suggest the authors acknowledge the argument if only to reject it and/or suggest the use of those (very safe and cheap) alternatives to true HBO while the evidence emerges more fully. This is a difficult situation. Perhaps the following reference may be useful in this regard: Bennett MH. Hyperbaric medicine and the placebo effect. Diving Hyperb Med. 2014 Dec 1;44(4):235-40.	We have refined our use of sham terminology and description of sham conditions, and have added further discussion of potential participation effects, which may occur in both treatment and control groups.
34	5	p.1, line 33: I am not convinced of the need for more sophisticated study designs – just better studies! Is this really a key finding?	We agree that better studies are needed, but also think that more sophisticated design and analysis could help clarify any potential effect of HBOT treatment.
35	5	p. 1, line 55: Same point as line 8 above.	The summary of findings in the executive summary have been revised with results from a newly added meta-analysis of the evidence.
36	5	p. 1, line 59: Same point again. Yes HBOT seems to improve symptoms but so does the sham exposure.	The summary of findings in the executive summary have been revised with results from a newly added meta-analysis of the evidence.
37	5	p. 2, line 15: Line 15: I understand the reason one might feel the applicability to veterans is low, but I am not sure I fully agree. Presumably Veterans have TBIs that are not related to blast injury, so this evidence applies to Veterans in that situation as much as it does to any other group.	We have revised the discussion of applicability to include applicability to Veterans sustaining non-blast severe TBIs.

38	5	p. 3, line 7: I do not see the evidentiary basis for saying an effect of HBO is likely. What is likely is that the observed improvements are due to a participation effect as attested to by the more or less equal efficacy of the sham exposures. I suggest a more accurate statement is that an effect of HBO is possible but unlikely.	We have revised the summary of findings with results from a newly added meta-analysis, and updated our findings with the conclusion that available evidence does not show HBOT leads to durable improvements in symptoms.
39	5	p. 3, line 10-11: I would substitute 'possible' for 'likely' here. If there is an HBO effect above the level of the general participation effect, then it is likely to be clinically unimportant.	We have revised the summary of findings with results from a newly added meta-analysis, and updated our findings with the conclusion that available evidence does not show HBOT leads to durable improvements in symptoms.
40	5	p. 3, line 13: I agree with the more sophisticated design suggestions for the most part, but I am not supportive of adjusting for baseline differences in severity. A stratified design would be better for that purpose I think. Properly powered studies using a universally accepted sham and on the basis of detecting the minimum clinically important effect are the most important features for the future.	We agree and have clarified that stratification by baseline severity and adjustment for other covariates would be optimal.
41	5	p. 4, line 25: This characterization of HBO is slightly inaccurate. It is not really 'designed to increase the supply of oxygen'. This and the subsequent text perpetuate the misunderstanding that HBO is all about the relief of hypoxia. This is part of the mechanism of action for some conditions, but there is a lot more to it than that. High oxygen tensions (pressures) in the blood and tissues result in a very complex suite of pharmacological effects that are only very loosely associated with the achievement of normoxia in previously hypoxic situations as your phrase suggests. For a brief outline of this I suggest the authors consider the appropriate section of the chapter in Harrison's Textbook of Medicine (Bennett MH, Mitchell SJ. Hyperbaric and Diving Medicine. In: Harrison's Principles of Internal Medicine Part 22, Chapter S11,20th Ed 2018). My suggestion is something like: "Hyperbaric oxygen therapy is designed to greatly increase the partial pressure of oxygen in the blood and tissues through the inhalation of pure oxygen in a pressurized environment. Most HBO regimens involve oxygen breathing at between 2 and 2.8 atmospheres and the resultant substantial increase in arterial oxygen partial pressure (often >1000 mmHg) has widespread physiologic and pharmacologic consequences. One direct consequence is the reversal of hypoxia in injured tissues, but others include pharmacologic effects that persist after removal from the pressure vessel, including changes in fibroblast and leukocyte function, the release of vasculogenic stem	We have revised this section to include these other mechanisms of HBOT and have reviewed the textbook chapter as a reference.

		cells from bone marrow and the upregulation of antioxidant defenses. Oxygen accelerates healing processes, reduces swelling and promotes cellular growth and repair.13,14,15"	
42	5	p. 4, line 36: Probably just a US usage I am not used to, but is 'urethrane' a common term for a plastic chamber? From Wikipedia I learn that '**Urethane** is most commonly **used** in a liquid form as a coating, adhesive, or sealant'. I am not aware of plastic chambers in use, but may be wrong about that! I do see online some references to chambers incorporating urethane coated components so I guess they could loosely be referred to as 'urethane chambers'.	We have removed the discussion of the different types of chambers to avoid confusion, as we are focusing on the medically used chambers.
43	5	p. 4, line 43: How about 'will have frequent interactions…'? Hard to see how this can be avoided and it is important of course.	We have removed "may" here for clarity that interactions with staff, etc. are inevitable.
44	5	p. 5, line 50: The statement here is a bit circular when one knows the background. The UHMS definition of the lower limit for HBOT is 1.4ATA precisely because that group wants (quite reasonably) to distinguish what they do as quite different from what is sometimes called 'mild HBO' – but should really be called mild hyperbaric therapy, mild oxygen-enriched air therapy or similar. Concerned about the claim that 1.2 or 1.3 ATA of air or oxygen-enriched air could be therapeutic, they changed the definition to exclude such 'treatments'. I suggest deleting 'and near the treatment threshold for HBOT (1.4 ATA)' to make a simpler and accurate statement. Also, it is a bit redundant as anything between 1.0 and 1.4 ATA will be 'near' 1.4. (of course, the 'sham' therapies used are air at these pressures rather than oxygen, so 1.4 ATA of air contains nowhere near the same oxygen pressure as 1.4 ATA of 100% oxygen). Many proponents of HBO for mTBI like to avoid this distinction.	We have deleted "and near the treatment threshold…" and added some further context to this section for clarity.
45	5	p. 5, line 52: It is worth noting that a therapeutic effect of 1.2 or 1.3 ATA of air would be absolutely extraordinary (as opposed to 100% oxygen at these pressures where such a notion is possible).	We have added a statement about the use of room air reducing the overall oxygen pressure in sham treatment.
46	5	p. 8, line 9: I presume the HBOT in the inclusion criteria is according to the UHMS definition?	Yes. We have added a statement about this for clarity.
47	5	p. 9, line 34: I understood that this RoB tool is only for the assessment of RCTs and not non-random comparative trials. There are validated instruments for the latter purpose. (Wells, G. et al. The Newcastle-Ottawa Scale (Nos) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. Ottawa Hospital Research Institute: Ottawa, ON, Canada.; Sterne JA, Hernán MA,	All of our included studies were randomized controlled trials or randomized crossover trials and so we used the RCT RoB tool.

		Reeves BC, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:1–7).	
48	5	Included studies: The relevant publications are very difficult to identify due to multiple reports of a number of trials – often for 'extra' outcomes not reported in the main paper. My apologies if the authors have seen all these, but potentially missed studies I have identified include: 1. Holbach KH, Wassman H, Kolberg T. Improved reversibility of the traumatic mid-brain syndrome following the use of hyperbaric oxygen. Acta Neurochirurgica 1974; 30:247-256. 2. Shandley S, Wolf EG, Schubert-Kappan CM, Baugh LM, Richards MF, Prye J, Arizpe HM, Kalns J. Increased circulating stem cells and better cognitive performance in traumatic brain injury subjects following hyperbaric oxygen therapy. Undersea & hyperbaric medicine: journal of the Undersea and Hyperbaric Medical Society, Inc. 2017;44(3):257-69. 3. Wares D, Cifu DX, Hole KW, Wetzel PA, Wares JR, Gitchel G, Carne W. Effects of hyperbaric oxygen on eye tracking abnormalities in males after mild traumatic brain injury. Journal of Rehabilitation Research and Development 2014;51(7):1047-1056 4. Churchill S, Miller RS, Deru K, Wilson SH, Weaver LK. Simple and procedural reaction time for mild traumatic brain injury in a hyperbaric oxygen clinical trial. Military Medicine. 2016 May 1;181(suppl_5):40-4.	1. Holbach KH, et al. – Unable to locate an English language full-text 2. Shandley S, et al. – Excluded as PTSD/Post-concussion symptom outcomes are only reported in relation to stem cell levels 3. Wares D, Cifu DX, et al. – We included the main outcomes from the Cifu study, but excluded this publication as we did not include eye tracking outcomes 4. Churchill S, et al. – We included the main outcomes from the Miller study (HOPPS), but excluded this publication as we did not focus on reaction time outcomes
49	5	p. 15, line 12-14: I think this statement is somewhat misleading given the complexity of this paper and the stated aim of being exploratory in order to identify good outcome measures for use in future trials. There were 71 participants and >600 outcomes calculated for this paper, with no attempts to statistically account for this large number – calling any interpretation of p-values or 95% CI into question. I think any conclusion that the HBOT group did better is highly qualified to say the least. I suggest modifying the description of the paper with some disscussion to this effect. (Appraisal of that paper is contained in the word document).	We have revised our synthesis of the results based on a newly added meta-analysis and have added some discussion of these methodological limitations of the analyses in the BIMA trial.
50	5	p. 16, line 25: Agree, but perhaps you should add the obvious problem previously mentioned of the facility in the design to promote a positive bias through a participation/placebo effect.	We have revised our synthesis of the results based on a newly added meta-analysis and have discussed the no comparator/standard care treatment separately, with an in-depth discussion

			of potential placebo/participation effects in the summary and discussion.
51	5	p. 23, line 48: I think this conclusion expressed in the first phrase is too strong given the evidence. Given the bias issues with RCTs not controlled with sham, and the very high number of comparisons made in BIMA, I think that such a benefit is possible rather than likely and if present likely to be evanescent. Although you do go on to explain in the next line that the benefits are likely to be due to a placebo effect, that modification comes too late. The enthusiastic proponents of HBO can and will selectively quote the first phrase in isolation.	We have revised our synthesis of the results based on a newly added meta-analysis and have added some discussion of these methodological limitations of the analyses in the BIMA trial.
52	5	p. 24, paragraph 1: Agree with your logic and that this is a very complicated area. Please consider adding that a universally agreed sham treatment that has been validated to be to be effective as a sham (ie not distinguishable from HBOT by participants) has an important role in clarifying the problems described here. This is under active discussion in the field.	We have added language on the need for consensus on treatment *and* sham protocols as a need for future research.
53	5	p. 25, line 51: I can't quite grasp how a crossover trial could possibly work given the therapeutic intention to show long-lasting benefit.	We have refined discussion of trial designs suggested for future research.
54	6	None. Excellent summary.	None
55	8	No additional suggestions, but the use of reports should have a test of quality, especially regarding the design and statistical rigor.	We have incorporated a meta-analysis to overcome some of the limitations in the analyses within individual studies, and expanded discussion of design and rigor of included trials.
56	8	When discussing the use of HBOT in acute severe TBI, it should be more strongly stated that the studies being describe are in the acute time after the injury and clinical state of the participants is vastly different than in chronic phase.	We have added clarification that the studies in severe TBI were in the acute time after injury and that this differs from the use of HBOT for (chronic) mild TBI.
57	8	*Second Review* Major improvement in analysis of the literature and assessment of limitations. Only additional information that should be included is: How many treatment sessions are required for HBOT approved indications, e.g., decompression sickness, gas embolism, CO poisoning, or soft tissue necrosis?	We have added a brief overview of the treatment protocols for the approved HBOT indications to the background section.
58	9	It seems important to note that this topic has been revisited multiple times over the last many years.	Comments addressed individually below.

		Major Concern: Whereas relevant evidence is presented, my major concern is with the Executive Summary and in particular the Key Findings.	
59	9	Key Findings: Bullet 1: "In patients with mild TBI and persistent post-concussion symptoms, current evidence suggests that HBOT can lead to short-term improvement in post-concussion and PTSD symptoms. It is unclear whether symptom improvements are clinically meaningful, and there is uncertainty in effects due to variations in patient, intervention, and comparator characteristics." What is missing from this is that "genuine treatment effects or placebo effects induced by the intensive nature of the HBOT intervention." Would most strongly recommend a revision of this bullet to include the information stated later in the summary. That is, similar findings were identified in the sham groups.	We have revised the summary of findings with results from a newly added meta-analysis, and updated our findings with the conclusion that available evidence does not show HBOT leads to durable improvements in symptoms.
60	9	Key Findings: Bullet 2: As noted, outcomes from this study are much more focused on measures related to hospitalization vs TBI-specific outcomes – this should be more strongly stated. That is, indications highlighted are more in line with "wound care" that HBOT has been found to be effective for vs longer-term functional TBI outcomes. Such treatments would be administered in the ICU or other acute settings.	We have added language to clarify that treatment was for hospitalized patients with acute injury.
61	9	Key Findings: Final Bullet: Additional information regarding the goals for future research would be helpful – in terms of mTBI and PTSD – findings appear to be consistent over many trials. It is unclear that future research is required. Might suggest that existing data could be used to evaluate the cost-effectiveness of HBOT for mild TBI and/or PTSD (vs traditional effective tx).	We have expanded on the goals of future research, which are to overcome some of the design and methodological limitations of the existing evidence and clarify any potential true effect of HBOT.
62	9	Background: Discussion of mechanisms (both related to TBI and PTSD) still remain elusive (see Xie et al 2007 – inflammation) – this does not appear to be sufficiently addressed in this brief.	We agree this is an important area to address and have added a discussion around future research on the etiologies of chronic post concussive symptoms to the discussion section.
63	9	Future Research: It is not clear to this reviewer that additional research to identify "small but clinically meaningful" change is warranted in light of current findings and evidence which suggests that patients with PTSD and/or mTBI DO benefit from more cost	We removed the statement regarding "well-conducted" trials and have expanded on how future research could overcome some of the design and methodological limitations of the

		effective – efficacious treatments for conditions on whole (PTSD: CPT; or specific symptoms, MTBI, insomnia, CBTi). As such further clarification regarding the basis for this recommendation would be useful. Moreover, within the Brief the "well-conducted, sham-controlled RCT's" are noted (p. 16). If further research were to be conducted, which this reviewer would NOT recommend, it is suggested that this work be conducted primarily by teams without clear conflicts related to outcomes.	existing evidence and clarify any potential true effect of HBOT. Future research is required by the Hannon Act, and so we feel recommendations for future research are warranted.
64	9	Page 2. "It is unclear whether observed short- and longer term symptom improvements among those with mTBI, regardless of PTSD status, are clinically meaningful." … or related to oxygen exposure	We have revised the executive summary with findings from a newly added meta-analysis to better reflect the findings from HBOT and sham conditions.
65	9	Page 4. Symptoms: some are overlapping and others are quite distinct (e.g., hypervigilance) this should be clarified.	We have revised the sentence on PTSD symptoms to distinguish between overlapping and unique symptoms.
66	9	Page 23. Line 6 – information re: similar improvements with SHAM is missing.	We have revised the discussion to more clearly state that similar improvements were seen in sham groups and to describe how this is likely the result of participation effects.
67	9	Figure 3. PTSD Module of SCID was use for Miller et al. Is this figure meant to be all inclusive?	This figure was not meant to be all inclusive, but to show common scales across studies. We have statements to clarify that these were "commonly" used scales or tools. In Miller et al, it appears the SCID tool was used for baseline PTSD assessment, but not outcome assessment, and so it was not included in the figure.

REFERENCES

1. Indications for Hyperbaric Oxygen Therapy. Undersea & Hyperbaric Medical Society. https://www.uhms.org/resources/hbo-indications.html. Updated 2020. Accessed December 21, 2020.
2. Piper S, Legross T, Murphy-Lavoie H. Idiopathic Sudden Sensorineural Hearing Loss (New! approved on October 8, 2011 by the UHMS Board of Directors. Undersear & Hyperbaric Medical Society. Indications for Hyperbaric Oxygen Therapy Web site. https://www.uhms.org/resources/hbo-indications.html. Updated 2020. Accessed.
3. Veterans Affairs/Department of Defense. Clinical Practice Guideline for The Management of Posttraumatic Stress Disorder and Acute Stress Disorder. 2017.
4. Veterans Affairs/Department of Defense. Clinical Practice Guidelines for The Management of Concussion-mild Traumatic Brain Injury (mTBI). 2016.
5. Colorado Division of Workers' Compensation. Traumatic Brain Injury Medical Treatment Guidelines. 2012.
6. Carney N, Totten AM, O'reilly C, et al. Guidelines for the management of severe traumatic brain injury. *Neurosurgery.* 2017;80(1):6-15.
7. Mathieu D, Marroni A, Kot J. Tenth European Consensus Conference on Hyperbaric Medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. *Diving Hyperb Med.* 2017;47(1):24-32.
8. Artru F, Chacornac R, Deleuze R. Hyperbaric oxygenation for severe head injuries. *European Neurology.* 1976;14(4):310-318.
9. Weaver LK, Wilson SH, Lindblad AS, et al. Hyperbaric oxygen for post-concussive symptoms in United States military service members: a randomized clinical trial. *Undersea Hyperb Med.* 2018;45(2):129-156.
10. Hart BB, Wilson SH, Churchill S, et al. Extended follow-up in a randomized trial of hyperbaric oxygen for persistent post-concussive symptoms. *Undersea Hyperb Med.* 2019;46(3):313-327.
11. Weaver LK, Churchill S, Wilson SH, Hebert D, Deru K, Lindblad AS. A composite outcome for mild traumatic brain injury in trials of hyperbaric oxygen. *Undersea Hyperb Med.* 2019;46(3):341-352.
12. Churchill S, Deru K, Weaver LK, et al. Adverse events and blinding in two randomized trials of hyperbaric oxygen for persistent post-concussive symptoms. *Undersea Hyperb Med.* 2019;46(3):331-340.
13. Boussi-Gross R, Golan H, Fishlev G, et al. Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury - randomized prospective trial. *PLoS ONE.* 2013;8(11):e79995.
14. Cifu DX, Hart BB, West SL, Walker W, Carne W. The effect of hyperbaric oxygen on persistent postconcussion symptoms. *Journal of Head Trauma Rehabilitation.* 2014;29(1):11-20.
15. Cifu DX, Walker WC, West SL, et al. Hyperbaric oxygen for blast-related postconcussion syndrome: three-month outcomes. *Ann Neurol.* 2014;75(2):277-286.
16. Walker WC, Franke LM, Cifu DX, Hart BB. Randomized, Sham-Controlled, Feasibility Trial of Hyperbaric Oxygen for Service Members With Postconcussion Syndrome: Cognitive and Psychomotor Outcomes 1 Week Postintervention. *Neurorehabil Neural Repair.* 2014;28(5):420-432.

17. Miller RS, Weaver LK, Bahraini N, et al. Effects of hyperbaric oxygen on symptoms and quality of life among service members with persistent postconcussion symptoms: a randomized clinical trial. *JAMA Internal Medicine.* 2015;175(1):43-52.
18. Harch PG, Andrews SR, Rowe CJ, et al. Hyperbaric oxygen therapy for mild traumatic brain injury persistent postconcussion syndrome: a randomized controlled trial. *Medical gas research.* 2020;10(1):8-20.
19. Lin J-W, Tsai J-T, Lee L-M, et al. Effect of hyperbaric oxygen on patients with traumatic brain injury. *Reconstructive Neurosurgery.* 2008:145-149.
20. Ren H, Wang W, Ge Z. Glasgow Coma Scale, brain electric activity mapping and Glasgow Outcome Scale after hyperbaric oxygen treatment of severe brain injury. *Chinese Journal of Traumatology= Zhonghua Chuang Shang Za Zhi.* 2001;4(4):239-241.
21. Rockswold G, Ford S. Preliminary results of a prospective randomized trial for treatment of severely brain-injured patients with hyperbaric oxygen. *Minnesota Medicine.* 1985;68(7):533-535.
22. Rockswold GL, Ford SE, Anderson DC, Bergman TA, Sherman RE. Results of a prospective randomized trial for treatment of severely brain-injured patients with hyperbaric oxygen. *Journal of Neurosurgery.* 1992;76(6):929-934.
23. Rockswold SB, Rockswold GL, Zaun DA, Liu J. A prospective, randomized Phase II clinical trial to evaluate the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity, and clinical outcome in severe traumatic brain injury. *Journal of Neurosurgery.* 2013;118(6):1317-1328.
24. Shi X, Tang Z, Xiong B, et al. Cerebral perfusion SPECT imaging for assessment of the effect of hyperbaric oxygen therapy on patients with postbrain injury neural status. *Chinese Journal of Traumatology= Zhonghua Chuang Shang Za Zhi.* 2003;6(6):346-349.
25. Wolf G, Cifu D, Baugh L, Carne W, Profenna L. The effect of hyperbaric oxygen on symptoms after mild traumatic brain injury. *Journal of Neurotrauma.* 2012;29(17):2606-2612.
26. Wolf EG, Prye J, Michaelson R, Brower G, Profenna L, Boneta O. Hyperbaric side effects in a traumatic brain injury randomized clinical trial. *Undersea Hyperb Med.* 2012;39(6):1075-1082.
27. Wolf EG, Baugh LM, Kabban CM, Richards MF, Prye J. Cognitive function in a traumatic brain injury hyperbaric oxygen randomized trial. *Undersea Hyperb Med.* 2015;42(4):313-332.
28. Xie Z, Zhuang M, Lin L, Xu H, Chen L, Hu L. Changes of plasma C-reactive protein in patients with craniocerebral injury before and after hyperbaric oxygenation. *Nerual Regen.* 2007;2(5):314-317.