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

Supplemental Materials

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Prepared for:
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APPENDIX A: FDA-CLEARED INDICATIONS FOR HBOT

FDA 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

FDA= US Food and Drug Administration

APPENDIX B: RELATED GUIDELINES

Organization Year	Title	Comments on HBOT in relation to TBI and/or PTSD
VA/DOD 2017[2]	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[3]	Clinical Practice Guideline for The Management of Concussion-mild Traumatic Brain Injury	NA
TRICARE 2015	TRICARE Policy Manual 6010.60-M	HBO therapy for Traumatic Brain Injury (TBI) is unproven.
Colorado Division of Workers' Compensation 2012[4]	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[5]	Guidelines for the Management of Severe Traumatic Brain Injury 4th Edition	Excluded studies on HBOT
Tenth European Consensus Conference on Hyperbaric Medicine 2017[6]	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)
UpToDate 2017	Hyperbaric Oxygen Therapy	No mention of PTSD or TBI

APPENDIX C: SEARCH STRATEGIES

1. Search for current systematic reviews (limited to 2012 forward) **Date Searched: 9/25/17**	
Sources:	**Evidence:**
AHRQ	Search: hyperbaric; HBOT Relevant Results: None
CADTH	Search: hyperbaric; HBOT Relevant Results: CADTH. (2014). Hyperbaric Oxygen Therapy for Adults with Mental Illness: A Review of the Clinical Effectiveness Rapid Response. Ottawa CA.
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
NLM	Search: hyperbaric; HBOT Relevant Results: None
ECRI Institute	Search: hyperbaric; HBOT Relevant Results: ECRI Institute. (2016). Hyperbaric Oxygen Therapy for Postconcussion Syndrome. ECRI Institute. (2016). Infusion Pumps to Consider for Use with Hyperbaric Chambers. ECRI Institute. (2016). Procurement Trends: Hyperbaric Chambers. ECRI Institute. (2017). Chambers, Hyperbaric.
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 C. http://art.puget-sound.med.va.gov/default.cfm Search: WHERE (dbo.tbl_D_VA_Site_Programs.Program_Code = 4) AND (Abstract LIKE "%hyperbaric%") OR (Abstract LIKE "%HBOT%") Relevant Results: None

MEDLINE: Systematic Reviews	Database: Ovid MEDLINE(R) <1946 to September Week 2 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <September 22, 2017> Search Strategy: --- 1 (hyperbaric or HBOT).mp. (16091) 2 exp Hyperbaric Oxygenation/ (11284) 3 1 or 2 (16091) 4 exp stress disorders, post-traumatic/ (27753) 5 exp combat disorders/ (2995) 6 (post-traumatic stress or posttraumatic stress or PTSD).mp. (28693) 7 exp craniocerebral trauma/ (147504) 8 exp Glasgow Coma Scale/ (8607) 9 exp Glasgow Outcome Scale/ (1673) 10 (mTBI or TBI).mp. (20497) 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. (161682) 12 concuss*.mp. (9804) 13 diffuse axonal injur*.mp. (1386) 14 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (16532) 15 Ranchos Los Amigos Scale.mp. (2) 16 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (270087) 17 3 and 16 (684) 18 limit 17 to english language (543) 19 limit 18 to yr="2012 -Current" (223) 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. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (294299) 21 "Review"/ or "Review Literature as Topic"/ (2372150) 22 20 or 21 (2504071) 23 19 and 22 (47) 24 remove duplicates from 23 (44) **********

PsycINFO	Database: PsycINFO <1806 to September Week 3 2017> Search Strategy: --- 1 (hyperbaric or HBOT).mp. (416) 2 exp Posttraumatic Stress Disorder/ (28129) 3 exp COMBAT EXPERIENCE/ (2578) 4 (post-traumatic stress or posttraumatic stress or PTSD).mp. (41382) 5 exp Traumatic Brain Injury/ (16247) 6 exp Brain Damage/ (33167) 7 exp Head Injuries/ (5705) 8 (mTBI or TBI).mp. (9934) 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. (49649) 10 concuss*.mp. (2864) 11 diffuse axonal injur*.mp. (295) 12 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (5322) 13 Ranchos Los Amigos Scale.mp. (11) 14 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (94430) 15 1 and 14 (85) 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. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (106761) 17 "Review"/ or "Review Literature as Topic"/ (22334) 18 16 or 17 (126869) 19 15 and 18 (6) 20 limit 19 to english language (5) **********
HTA	Database: EBM Reviews - Health Technology Assessment <4th Quarter 2016> Search Strategy: --- 1 (hyperbaric or HBOT).mp. (54) 2 exp Hyperbaric Oxygenation/ (49) 3 1 or 2 (54)

	4 exp stress disorders, post-traumatic/ (28) 5 exp combat disorders/ (2) 6 (post-traumatic stress or posttraumatic stress or PTSD).mp. (31) 7 exp craniocerebral trauma/ (45) 8 exp Glasgow Coma Scale/ (1) 9 exp Glasgow Outcome Scale/ (0) 10 (mTBI or TBI).mp. (12) 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. (78) 12 concuss*.mp. (5) 13 diffuse axonal injur*.mp. (0) 14 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (4) 15 Ranchos Los Amigos Scale.mp. (0) 16 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (123) 17 3 and 16 (5) 18 limit 17 to english language (5) 19 limit 18 to yr="2012 -Current" (0) **********
Cochrane Database of Systematic Reviews & Cochrane Methodology Register	Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 20, 2017>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012> Search Strategy: --- 1 (hyperbaric or HBOT).mp. (88) 2 (post-traumatic stress or posttraumatic stress or PTSD).mp. (167) 3 (mTBI or TBI).mp. (72) 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. (674) 5 concuss*.mp. (43) 6 diffuse axonal injur*.mp. (35) 7 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (112) 8 Ranchos Los Amigos Scale.mp. (0) 9 2 or 3 or 4 or 5 or 6 or 7 or 8 (880) 10 1 and 9 (17) 11 limit 10 to yr="2012 -Current" (13) **********
Database of Randomized Controlled Trials in Hyperbaric Medicine	Search: Posttraumatic; post traumatic; PTSD; TBI; brain injury; head injury Relevant Results: None
Systematic Reviews (Journal)	Search: hyperbaric; HBOT Relevant Results: None

2. Systematic reviews currently under development (forthcoming reviews & protocols) **Date Searched: 9/25/17**	
Sources:	**Evidence:**
PROSPERO (SR registry)	http://www.crd.york.ac.uk/PROSPERO/ Search: Hyperbaric; HBOT

	Relevant Results: Yan Dong. The effect of hyperbaric oxygen therapy on post-concussion syndrome: a systematic review and meta-analysis. PROSPERO 2016:CRD42016032620 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016032620 Miloslav Klugar, Ivana Nytra, Sona Bocková, Jitka Klugarová, Zuzana Kelnarová, Jana Marecková. The effectiveness of hyperbaric oxygen therapy on mortality in adults with craniotrauma: a systematic review protocol. PROSPERO 2015:CRD42015016547 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015016547
DoPHER (SR Protocols)	Search: Hyperbaric; HBOT Relevant Results: None

3. Current Guidelines **Date Searched: 9/22/17**	
Sources:	**Evidence:**
VA/DoD Clinical Practice Guidelines	Relevant Results: VA/DoD. (2016). Clinical Practice Guidelines for The Management of Concussion-mild Traumatic Brain Injury (mTBI). VA/DoD. (2017). Clinical Practice Guideline for The Management of Posttraumatic Stress Disorder and Acute Stress Disorder.
National Guideline Clearinghouse	Search: hyperbaric; HBOT; traumatic brain injury; TBI; post-traumatic stress syndrome; PTSD Relevant Results: Colorado Division of Workers' Compensation Traumatic Brain Injury Medical Treatment Guidelines (2012)
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) <1946 to September Week 2 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <September 21, 2017> Search Strategy: --- 1 (hyperbaric or HBOT).mp. (16091)

	2 exp Hyperbaric Oxygenation/ (11284) 3 1 or 2 (16091) 4 exp stress disorders, post-traumatic/ (27753) 5 exp combat disorders/ (2995) 6 (post-traumatic stress or posttraumatic stress or PTSD).mp. (28689) 7 exp craniocerebral trauma/ (147504) 8 exp Glasgow Coma Scale/ (8607) 9 exp Glasgow Outcome Scale/ (1673) 10 (mTBI or TBI).mp. (20491) 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. (161659) 12 concuss*.mp. (9803) 13 diffuse axonal injur*.mp. (1386) 14 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (16528) 15 Ranchos Los Amigos Scale.mp. (2) 16 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (270057) 17 3 and 16 (684) 18 limit 17 to english language (543) 19 exp Guideline/ (30968) 20 guideline*.mp. (381513) 21 19 or 20 (381513) 22 18 and 21 (9) **********
UpToDate	Search: Hyperbaric; HBOT Relevant Results: https://www.uptodate.com/contents/hyperbaric-oxygen-therapy

4. Current primary literature (limited to 2014 forward) **Date Searched: 9/25/17**	
Sources:	**Search Strategy/ Evidence:**
Medline	Database: Ovid MEDLINE(R) <1946 to September Week 2 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <September 22, 2017> Search Strategy: --- 1 (hyperbaric or HBOT).mp. (16091) 2 exp Hyperbaric Oxygenation/ (11284) 3 1 or 2 (16091) 4 exp stress disorders, post-traumatic/ (27753) 5 exp combat disorders/ (2995) 6 (post-traumatic stress or posttraumatic stress or PTSD).mp. (28693) 7 exp craniocerebral trauma/ (147504) 8 exp Glasgow Coma Scale/ (8607) 9 exp Glasgow Outcome Scale/ (1673) 10 (mTBI or TBI).mp. (20497) 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. (161682) 12 concuss*.mp. (9804) 13 diffuse axonal injur*.mp. (1386) 14 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (16532) 15 Ranchos Los Amigos Scale.mp. (2)

	16 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (270087) 17 3 and 16 (684) 18 limit 17 to english language (543) 19 limit 18 to yr="2014 -Current" (151) 20 remove duplicates from 19 (144) **********
Medline: Harms Date searched: 9/26/17	Database: Ovid MEDLINE(R) <1946 to September Week 2 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <September 25, 2017> Search Strategy: --- 1 exp Patient Harm/ (103) 2 harm*.mp. (144083) 3 exp Long Term Adverse Effects/ (265) 4 adverse effect*.mp. (135692) 5 1 or 2 or 3 or 4 (276407) 6 (hyperbaric or HBOT).mp. (16093) 7 exp Hyperbaric Oxygenation/ (11284) 8 6 or 7 (16093) 9 exp stress disorders, post-traumatic/ (27753) 10 exp combat disorders/ (2995) 11 (post-traumatic stress or posttraumatic stress or PTSD).mp. (28708) 12 exp craniocerebral trauma/ (147504) 13 exp Glasgow Coma Scale/ (8607) 14 exp Glasgow Outcome Scale/ (1673) 15 (mTBI or TBI).mp. (20505) 16 ((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. (161723) 17 concuss*.mp. (9809) 18 diffuse axonal injur*.mp. (1387) 19 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (16533) 20 Ranchos Los Amigos Scale.mp. (2) 21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (270148) 22 8 and 21 (684) 23 limit 22 to english language (543) 24 5 and 23 (13) **********
PsychINFO	Database: PsycINFO <1806 to September Week 3 2017> Search Strategy: --- 1 (hyperbaric or HBOT).mp. (416) 2 exp Posttraumatic Stress Disorder/ (28129) 3 exp COMBAT EXPERIENCE/ (2578) 4 (post-traumatic stress or posttraumatic stress or PTSD).mp. (41382) 5 exp Traumatic Brain Injury/ (16247) 6 exp Brain Damage/ (33167) 7 exp Head Injuries/ (5705) 8 (mTBI or TBI).mp. (9934) 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. (49649) 10 concuss*.mp. (2864) 11 diffuse axonal injur*.mp. (295) 12 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (5322) 13 Ranchos Los Amigos Scale.mp. (11)

	14 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (94430) 15 1 and 14 (85) 16 limit 15 to english language (81) 17 limit 16 to yr="2014 -Current" (29) **********
CCRCT	Database: EBM Reviews - Cochrane Central Register of Controlled Trials <August 2017> Search Strategy: --- 1 (hyperbaric or HBOT).mp. (2071) 2 exp Hyperbaric Oxygenation/ (317) 3 1 or 2 (2071) 4 exp stress disorders, post-traumatic/ (1231) 5 exp combat disorders/ (94) 6 (post-traumatic stress or posttraumatic stress or PTSD).mp. (2807) 7 exp craniocerebral trauma/ (2031) 8 exp Glasgow Coma Scale/ (389) 9 exp Glasgow Outcome Scale/ (122) 10 (mTBI or TBI).mp. (1390) 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. (5210) 12 concuss*.mp. (311) 13 diffuse axonal injur*.mp. (36) 14 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (1554) 15 Ranchos Los Amigos Scale.mp. (0) 16 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (9822) 17 3 and 16 (65) 18 limit 17 to english language (37) 19 limit 18 to yr="2014 -Current" (18) 20 remove duplicates from 19 (18) **********
Google Scholar	Search: Hyperbaric; HBOT Relevant Results: Hexdall, E., Brave, R., Kraft, K., & Siewers, J. (2016). Diving deep into hyperbaric oxygen therapy. Nursing, 46(10), 28.
Pedro	Search: Hyperbaric; HBOT (limited to 2012 forward due to potential for systematic review results) Relevant Results: None
PILOTS	Search: hyperbaric* OR HBOT (limited to 2012 forward due to potential for systematic review results) Relevant Results: None
The Database of Randomised Controlled Trials in Diving and Hyperbaric Medicine	Relevant Results: None previously uncaptured

5. Primary literature currently under development (forthcoming studies & protocols) **Date Searched: 9/26/17**	
Sources:	**Search Strategy/ Evidence:**
Clinicaltrials.gov	Search: Hyperbaric or HBOT Relevant Results: NCT01611194 (Completed, outcome results not yet published) NCT01847755 (Currently recruiting) NCT02089594 (Currently recruiting) NCT00594503 (Currently recruiting) NCT02407028 (Not yet recruiting) NCT01105962 (Terminated)
UK Clinical Trials Gateway	Search: Hyperbaric; HBOT Relevant results: None
WHO International Clinical Trials Registry Platform	Search: Hyperbaric or HBOT Relevant results: Magnetic resonance imaging study of hyperbaric oxygen treatment on cognitive dysfunction after traumatic brain injury (Currently recruiting, China)

6. Advocacy Groups (HBOT, PTSD, and TBI) **Date Searched: 9/22/17**	
Sources:	**Search Strategy/ Evidence:**
Brain Injury Association of America	Search: hyperbaric; HBOT Relevant Results: None
Kesssler 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: 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
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. Update Search **Date Searched: 1/4/18**	
Sources:	**Search Strategy/ Evidence:**

Medline	Database: Ovid MEDLINE(R) <1946 to December Week 4 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <January 03, 2018> Search Strategy: --- 1 (hyperbaric or HBOT).mp. (16753) 2 exp Hyperbaric Oxygenation/ (11750) 3 1 or 2 (16753) 4 exp stress disorders, post-traumatic/ (29627) 5 exp combat disorders/ (3096) 6 (post-traumatic stress or posttraumatic stress or PTSD).mp. (30638) 7 exp craniocerebral trauma/ (155026) 8 exp Glasgow Coma Scale/ (9337) 9 exp Glasgow Outcome Scale/ (1913) 10 (mTBI or TBI).mp. (21919) 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. (171008) 12 concuss*.mp. (10439) 13 diffuse axonal injur*.mp. (1489) 14 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (17960) 15 Ranchos Los Amigos Scale.mp. (2) 16 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (285478) 17 3 and 16 (718) 18 limit 17 to english language (575) 19 limit 18 to yr="2017 -Current" (27) 20 remove duplicates from 19 (26) ********** Relevant Results: None
PsychINFO	Database: PsycINFO <1806 to December Week 4 2017> Search Strategy: --- 1 (hyperbaric or HBOT).mp. (423) 2 exp Posttraumatic Stress Disorder/ (28560) 3 exp COMBAT EXPERIENCE/ (2604) 4 (post-traumatic stress or posttraumatic stress or PTSD).mp. (42204) 5 exp Traumatic Brain Injury/ (16636) 6 exp Brain Damage/ (33600) 7 exp Head Injuries/ (5772) 8 (mTBI or TBI).mp. (10195) 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. (50355) 10 concuss*.mp. (2979) 11 diffuse axonal injur*.mp. (305) 12 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (5435) 13 Ranchos Los Amigos Scale.mp. (11) 14 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (95998) 15 1 and 14 (88) 16 limit 15 to english language (84) 17 limit 16 to yr="2017 -Current" (8) ********** Relevant Results: None

CCRCT	Database: EBM Reviews - Cochrane Central Register of Controlled Trials <November 2017> Search Strategy: --- 1 (hyperbaric or HBOT).mp. (2096) 2 exp Hyperbaric Oxygenation/ (317) 3 1 or 2 (2096) 4 exp stress disorders, post-traumatic/ (1269) 5 exp combat disorders/ (96) 6 (post-traumatic stress or posttraumatic stress or PTSD).mp. (2919) 7 exp craniocerebral trauma/ (2057) 8 exp Glasgow Coma Scale/ (397) 9 exp Glasgow Outcome Scale/ (124) 10 (mTBI or TBI).mp. (1472) 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. (5408) 12 concuss*.mp. (328) 13 diffuse axonal injur*.mp. (39) 14 (Glasgow adj (coma or outcome) adj (scale* or score*)).mp. (1608) 15 Ranchos Los Amigos Scale.mp. (0) 16 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (10162) 17 3 and 16 (66) 18 limit 17 to english language (38) 19 limit 18 to yr="2017 -Current" (5) 20 remove duplicates from 19 (5) ********** Relevant Results: None
Database of Randomized Controlled Trials in Hyperbaric Medicine	Search: Posttraumatic; post traumatic; PTSD; TBI; brain injury; head injury Relevant Results: None
Pedro	Search: Hyperbaric; HBOT (limited to 2012 forward due to potential for systematic review results) Relevant Results: None
PILOTS	Search: hyperbaric* OR HBOT (limited to 2012 forward due to potential for systematic review results) Relevant Results: None

APPENDIX D: LIST OF EXCLUDED STUDIES

Exclude reasons: 1=Ineligible population, 2=Ineligible intervention, 3=Ineligible comparator, 4=Intermediate outcome (*ie*, stem cell markers, angiogenesis), 5=Ineligible timing, 6=Ineligible study design, 7=Ineligible publication type, 8=Outdated or unclear or high risk of bias SR, 9=Non-English language, 10=Critique or rebuttal of paper, 11=Unable to locate full-text, B=Background, G=Guidelines

#	Citation	Exclude reason
1	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.	B
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 Journal of Surgery. 2006;76(3):163-174.	E7
3	Adams E. Hyperbaric Oxygen Therapy for Traumatic Brain Injury and Post Traumatic Stress Disorder. VA Technology Assessment Program. 2010.	B
4	Algattas H, Huang JH. Traumatic Brain Injury pathophysiology and treatments: early, intermediate, and late phases post-injury. International Journal of Molecular Sciences. 2013;15(1):309-341.	E7
5	Algattas H, Huang JH. Neurotrauma and Repair Research: Traumatic Brain Injury (TBI) and its Treatments. Biomedical Engineering & Computational Biology. 2013;5:51-56.	B
6	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
7	Bennett MH. Hyperbaric medicine and the placebo effect. Diving & Hyperbaric Medicine. 2014;44(4):235-240.	B
8	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
9	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
10	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
11	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 brain injury association. Netherlands. Conference start:. 20160302. Conference end: 20160305 30(5-6):729.	E7
12	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
13	Carney N, Totten AM, O'reilly C, et al. Guidelines for the management of severe traumatic brain injury. Neurosurgery. 2017;80(1):6-15.	G

#	Citation	Exclude reason
14	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;181(5 Suppl):40-44.	E4
15	Colorado Division of Workers' Compensation. Traumatic Brain Injury Medical Treatment Guidelines. 2012.	G
16	Cossu G. Therapeutic options to enhance coma arousal after traumatic brain injury: state of the art of current treatments to improve coma recovery. British Journal of Neurosurgery. 2014;28(2):187-198.	E4
17	ECRI Institute. Hyperbaric Oxygen Therapy for Postconcussion Syndrome. 2016.	E8
18	ECRI Institute. Procurement Trends: Hyperbaric Chambers - May, 2016. 2016.	B
19	ECRI Institute. Infusion Pumps to Consider for Use with Hyperbaric Chambers. 2016.	E2
20	ECRI Institute. Chambers, Hyperbaric. 2017.	B
21	Efrati S, Ben-Jacob E. Reflections on the neurotherapeutic effects of hyperbaric oxygen. Expert Review of Neurotherapeutics. 2014;14(3):233-236.	E7
22	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. Neuropsychiatric Disease & Treatment. 2016;12:2689-2705.	B
23	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.	B
24	Figueroa XA, Wright JK. Clinical results in brain injury trials using HBO2 therapy: Another perspective. Undersea & Hyperbaric Medicine. 2015;42(4):333-351.	B
25	Figueroa XA, Wright JK. Hyperbaric oxygen: B-level evidence in mild traumatic brain injury clinical trials. Neurology. 2016;87(13):1400-1406.	B
26	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
27	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.	B
28	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. Pharmaceutical Statistics. 2016;15(5):396-404.	B
29	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 Review of Neurotherapeutics. 2016;16(1):61-70.	B
30	Hadanny A, Efrati S. Oxygen--a limiting factor for brain recovery. Critical Care (London, England). 2015;19:307.	E7
31	Hadanny A, Efrati S. Treatment of persistent post-concussion syndrome due to mild traumatic brain injury: current status and future directions. Expert Review of Neurotherapeutics. 2016;16(8):875-887.	B
32	Hadanny A, Efrati S. The efficacy and safety of hyperbaric oxygen therapy in traumatic brain injury. Expert Review of Neurotherapeutics. 2016;16(4):359-360.	E10
33	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 & Hyperbaric Medicine. 2016;43(1):21-28.	E1
34	Hampson NB, Holm J. "Hyperbaric oxygen: B-level evidence in mild traumatic brain injury clinical trials": Comment. Neurology. 2017;89(7):750.	E10

#	Citation	Exclude reason
35	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.	E10
36	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.	E10
37	Harch PG. Hyperbaric oxygen in chronic traumatic brain injury: oxygen, pressure, and gene therapy. Medical Gas Research. 2015;5:9.	B
38	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.	B
39	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.	B
40	Hawkins JR, Gonzalez KE, Heumann KJ. The Effectiveness of Hyperbaric Oxygen Therapy as a Treatment for Postconcussion Symptoms. Journal of Sport Rehabilitation. 2017;26(3):290-294.	E8
41	Hexdall E, Brave R, Kraft K, Siewers J. Diving deep into hyperbaric oxygen therapy. Nursing. 2016;46(10):28.	B
42	Hoge CW, Jonas WB. Hyperbaric Oxygen Treatment for Persistent Postconcussion Symptoms--Reply. JAMA Internal Medicine. 2015;175(7):1241.	E10
43	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.	E10
44	Hooker JS. Hyperbaric Oxygen Therapy: Using Evidence-Based Medicine to Heal Injured Brain Tissue. North Carolina Medical Journal. 2016;77(1):69-70.	B
45	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.	E10
46	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
47	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.	B
48	Karam C, Griggs RC. "Hyperbaric oxygen: B-level evidence in mild traumatic brain injury clinical trials": Editors' note. Neurology. 2017;89(7):750.	E10
49	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
50	Kohlenberg A, Mody K. Hyperbaric oxygen for post-concussion symptoms secondary to mild traumatic brain injury. Clinical journal of sport medicine.24(2):193.	E7
51	Korley F, Rockswold G, Gajewski B, Martin R, Silbergleit R, Barsan W. The design of the hyperbaric oxygen brain injury treatment (Hobit) trial. Journal of neurotrauma. 2017;Conference: 35th annual national neurotrauma symposium. United states. 34(13):A59-A60.	B
52	Marois P, Mukherjee A, Ballaz L. Hyperbaric Oxygen Treatment for Persistent Postconcussion Symptoms--A Placebo Effect? JAMA Internal Medicine. 2015;175(7):1239-1240.	E10

#	Citation	Exclude reason
53	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 & Hyperbaric Medicine. 2017;47(1):24-32.	G
54	McCrary BF, Weaver L, Marrs K, et al. Hyperbaric oxygen (HBO2) for post-concussive syndrome/chronic TBI--product summary. Undersea & Hyperbaric Medicine. 2013;40(5):443-467.	B
55	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
56	McMonnies CW. Hyperbaric oxygen therapy and the possibility of ocular complications or contraindications. Clinical and Experimental Optometry. 2015;98(2):122-125.	B
57	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.	B
58	Miller RS, Weaver LK, Brenner LA. Hyperbaric Oxygen Treatment for Persistent Postconcussion Symptoms--Reply. JAMA Internal Medicine. 2015;175(7):1240-1241.	E10
59	Mitchell SJ, Bennett MH. Unestablished indications for hyperbaric oxygen therapy. Diving & Hyperbaric Medicine. 2014;44(4):228-234.	B
60	Sawyer Q, Vesci B, McLeod TC. Physical Activity and Intermittent Postconcussion Symptoms After a Period of Symptom-Limited Physical and Cognitive Rest. Journal of Athletic Training. 2016;51(9):739-742.	E2
61	Schnurr PP, Hermann BA, Mott JM. Clinician's Trauma Update, December 2014. 2014;8:1-3.	E7
62	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 & Hyperbaric Medicine. 2017;44(3):257-269.	E4
63	Skipper LD, Churchill S, Wilson SH, Deru K, Labutta RJ, Hart BB. Hyperbaric oxygen for persistent post-concussive symptoms: long-term follow-up. Undersea & Hyperbaric Medicine. 2016;43(5):601-613.	E4
64	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.	B
65	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. Restorative Neurology & Neuroscience. 2015;33(6):943-951.	E4
66	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. Frontiers in Human Neuroscience. 2017;11:508.	E4
67	The American Legion TBI/PTSD Ad Hoc Committee. The War Within: Treatment of Traumatic Brain Injury and Post Traumatic Stress Disorder. 2013.	E7
68	TreatNow. HBOT Research and Science. 2017.	B
69	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
70	United States Government Accountability Office. Research on Hyperbaric Oxygen Therapy to Treat Traumatic Brain Injury and Post-Traumatic Stress Disorder. 2015.	B

#	Citation	Exclude reason
71	Veterans Affairs/Department of Defense. Clinical Practice Guidelines for The Management of Concussion-mild Traumatic Brain Injury (mTBI). 2016.	G
72	Veterans Affairs/Department of Defense. Clinical Practice Guideline for The Management of Posttraumatic Stress Disorder and Acute Stress Disorder. 2017.	G
73	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
74	Weaver LK, Cifu D, Hart B, Wolf G, Miller S. Hyperbaric oxygen for post-concussion syndrome: design of Department of Defense clinical trials. Undersea & Hyperbaric Medicine. 2012;39(4):807-814.	B
75	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 & Hyperbaric Medicine. 2016;43(5):521-530.	B
76	Williams CS, Weaver LK, Lindblad AS, Kumar S, Langford DR. Baseline neurological evaluations in a hyperbaric trial of post-concussive syndrome. Undersea & Hyperbaric Medicine. 2016;43(5):511-519.	E4
77	Wilson SH, Weaver LK, Lindblad AS. Neuropsychological assessments in a hyperbaric trial of post-concussive symptoms. Undersea & Hyperbaric Medicine. 2016;43(5):585-599.	B
78	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. Pakistan Journal of Pharmaceutical Sciences. 2016;29(1 Suppl):273-280.	E4

APPENDIX E: EVIDENCE TABLES

DATA ABSTRACTION OF INCLUDED SYSTEMATIC REVIEWS

Author Year # Studies # Patients	Objective Selection criteria	Search Date Databases searched QA Tool	Patient Characteristics	Overall Mortality Rate (HBOT vs Control)	GOS Improvement Rate (HBOT vs Control)	Change in PTSD Score (HBOT - Control)	Adverse Events
Bennett 2012[7] # Studies= 7 # Patients= 571	To assess the effects of adjunctive HBOT for acute traumatic brain injury in persons admitted to an intensive care or intensive neurosurgical facility with an acute TBI following blunt trauma Randomized studies comparing the effect of therapeutic regimens which included HBOT with those that did not, for people with traumatic brain injury.	March 2012 CENTRAL, MEDLINE, EMBASE, CINAHL, Database of Randomized Controlled Trials in Hyperbaric Medicine Cochrane Collaboration's tool for assessing risk of bias in randomized trials	Moderate and Severe TBI with or without PTSD RCTs did not include service members or Veterans Mean age range: NR Sex (male): NR	RR= 0.69 (95% CI= 0.54 to 0.88)	RR= 1.94 (95% CI= 0.92 to 4.08)	NR	Severe pulmonary complications: RR= 15.57 (95% CI= 2.11 to 114.72); NNH= 8 95% CI= 5 to 15) Seizure: RR= 5.0 (95% CI= 0.24 to 102.6) Middle ear barotrauma: RR= 5.0 (95% CI= 0.24 to 102.6)
Crawford 2017[8] # Studies= 12 # Patients= 1,056	This systematic review examines the efficacy of hyperbaric oxygen (HBO2) for traumatic brain injury (TBI) to make evidence-based recommendations for its application and future research Peer-reviewed study designs presented in the English language; involving subjects suffering from the	December 2014 PubMed, CINAHL, PsycInfo, and Cochrane, Database of Randomized Controlled Trials in Hyperbaric Medicine Scottish Intercollegiate Guidelines	Mild, Moderate, and Severe TBI with or without PTSD Select RCTs included service members and Veterans Mean age range: NR Sex (male): NR	Two low (0) quality RCTs found no statistically significant differences between HBO2 and "standard care" groups.	In 2 acceptable (+) quality RCTs, the HBO2 groups showed statistically significant better scores versus "standard care", whereas the third RCT found no statistically significant differences.	One acceptable (+) quality RCT reported improvements in mean change scores tended to favor sham vs. HBO2 at post-intervention. P-values not reported.	3 of 4 RCTs involving mTBI and 3 of 7 RCTs involving moderate-severe TBI populations describe adverse events. These reports describe various ear problems including barotrauma, severe ear pain (resolved by tympanostomy) and hemotympanum; nausea; sinus squeeze and sinus pain; claustrophobia; headache; musculoskeletal chest pain; tooth pain;

Author Year # Studies # Patients	Objective Selection criteria	Search Date Databases searched QA Tool	Patient Characteristics	Overall Mortality Rate (HBOT vs Control)	GOS Improvement Rate (HBOT vs Control)	Change in PTSD Score (HBOT - Control)	Adverse Events
	consequences of TBI in both military and civilian populations; and HBO2 is being used as the intervention without preexisting conditions.	Network Checklist for RCTs (SIGN 50)					transient worsening of myopia; pulmonary adverse events; and the occurrence of seizures.
Wang 2016[9] # Studies= 8 # Patients= 519	The present meta-analysis evaluated the outcomes of HBOT in patients with traumatic brain injury (TBI). Randomized, controlled trials or two-arm prospective studies comparing normobaric vs hyperbaric oxygen therapy in patients with either severe (GCS score 3–8) or mild (GCS score 13–15) traumatic brain injury with PCS symptoms were included in the current meta-analysis.	December 10, 2014 Medline, Cochrane, EMBASE, Google Scholar Cochrane Collaboration's tool for assessing risk of bias in randomized trials	Mild, Moderate, and Severe TBI with or without PTSD Select RCTs included service members and Veterans Mean age range: 23 to 40 Sex (male): 62% to 100%	OR (FE)= 0.32 (95% CI= 0.18 to 0.57) in moderate-severe TBI from 3 overall good quality RCTs	OR (RE)= 3.78 (95% CI= 1.23 to 11.63) in moderate-severe TBI from 3 overall good quality RCTs* *Significance was driven by a single RCT	Mean change (FE)= -1.49 (95% CI= -5.79 to 2.80) in mTBI from 2 overall good quality RCTs	NR

Abbreviations: GCS=Glasgow Coma Score, Glasgow Outcome Score, HBOT=hyperbaric oxygen therapy, NNH=number needed to heal, PCS=post-concussion syndrome, PTSD=post-traumatic stress disorder, TBI=traumatic brain injury

QUALITY ASSESSMENT OF INCLUDED SYSTEMATIC REVIEWS

Bennett 2012[7]		
Domain	**Concern (Low/High/Unclear)**	**Rationale for Concern**
1. Study eligibility criteria	Low	Review adhered to clearly stated pre-defined objectives and eligibility criteria, which were appropriate for the review question No inappropriate restrictions in eligibility criteria
2. Identification and selection of studies	Low	Appropriate range of databases searched Independent screening by 3 authors Appropriate restrictions regarding dates and language Appropriate methods for identifying additional studies (reviewing article references) and minimizing error (multiple reviewers)
3. Data collection and study appraisal	Low	Collected data using a prespecified template Data extraction was reviewed for accuracy Study quality was assessed using the Cochrane Risk of Bias tool Unclear if quality analysis was dual independent
4. Synthesis and findings	Low	All predefined analyses conducted on eligible studies, heterogeneity described, biases addressed in synthesis Quantitative synthesis was conducted as appropriate
5. Overall Risk of Bias		
Did the interpretation of findings address all the concerns identified in Domains 1 to 4? (Y/ N/ NI)		Y
Was the relevance of identified studies to the review's research question appropriately considered? (Y/ N/ NI)		Y
Did the reviewers avoid emphasizing results based on their statistical significance? (Y/ N/ NI)		Y
Risk of bias in the review (Low/ High/ Unclear)		Low
Rationale for risk		Clear methods outlined for study eligibility criteria, search, study selection, and data abstraction. Quality assessment performed using a risk of bias tool, but it was unclear if it was reviewed for accuracy. The review conclusions accurately reflect the results.

Crawford 2017[8]		
Domain	**Concern (Low/High/Unclear)**	**Rationale for Concern**
1. Study eligibility criteria	Low	Review adhered to clearly stated pre-defined objectives and eligibility criteria, which were appropriate for the review question
2. Identification and selection of studies	Low	Multiple databases searched; Appropriate restrictions on dates and language; dual independent screening to minimize error in study selection
3. Data collection and study appraisal	Low	Followed Common Data Element Project's classification of outcomes for data abstraction; unclear if dual review of data abstraction; dual independent quality assessment of RCTs
4. Synthesis and findings	Low	All predefined analyses conducted on eligible studies; Qualitative synthesis was appropriate given the heterogeneity of comparators across studies
5. Overall Risk of Bias		
Did the interpretation of findings address all the concerns identified in Domains 1 to 4? (Y/ N/ NI)		Y
Was the relevance of identified studies to the review's research question appropriately considered? (Y/ N/ NI)		Y
Did the reviewers avoid emphasizing results based on their statistical significance? (Y/ N/ NI)		Y
Risk of bias in the review (Low/ High/ Unclear)		Low
Rationale for risk		Clear methods outlined for study eligibility criteria, search, study selection, and quality assessment. Data was collected following prespecified criteria, but it was unclear if data abstraction was reviewed for accuracy. The review conclusions accurately reflect the results.

Wang 2016[9]		
Domain	**Concern (Low/High/Unclear)**	**Rationale for Concern**
1. Study eligibility criteria	Low	Review adhered to clearly stated pre-defined objectives and eligibility criteria, which were appropriate for the review question
2. Identification and selection of studies	Low	Multiple databases searched; reasonable restrictions on study design; dual independent screening to minimize error in study selection
3. Data collection and study appraisal	Low	Quality assessed using pre-specified tool, unclear if dual review of quality assessment; dual independent data collection
4. Synthesis and findings	Low	Synthesis methods pre-specified; Meta-analysis included all studies; Sensitivity and heterogeneity assessed
5. Overall Risk of Bias		
Did the interpretation of findings address all the concerns identified in Domains 1 to 4? (Y/ N/ NI)		Y
Was the relevance of identified studies to the review's research question appropriately considered? (Y/ N/ NI)		Y
Did the reviewers avoid emphasizing results based on their statistical significance? (Y/ N/ NI)		Y
Risk of bias in the review (Low/ High/ Unclear)		Low
Rationale for risk		Clear methods outlined for study eligibility criteria, search, study selection, data abstraction, and meta-analysis. Study quality assessment was done, but it was unclear if it was reviewed for accuracy. The review conclusions accurately reflect the results.

QUALITY ASSESSMENT OF SUBSET OF INCLUDED PRIMARY STUDIES

Quality Assessment of RCTs

Author Year	Randomization adequate? Adequate allocation concealment?	Groups similar at baseline?	Outcome assessors, care provider, patient masked?	Outcome measurement equal, reliable, and valid?	Intention-to-treat (ITT) analysis?	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality
Boussi-Gross 2013[10]	Unclear; Not described Unclear; Not described	Yes 2 years more education in the treatment group	Yes No No	Yes	No	Unclear Adherence to HBOT protocol not described	No Intervention group= 28.9% Crossover group= 46.7%	Fair
Miller 2015[11]	Yes; Permutated block method Unclear; Not described	Yes	Yes Yes Yes	Yes	Yes Exclusion of <5% of patients from analysis	Yes All but 2 did not receive intervention	Yes Intervention group= 4% (1/24) Sham group= 16% (4/25) Control group= 13% (3/23)	Fair
Ren 2001[12,13]	Unclear; Not described Unclear; Not described	Unclear No statistical testing at baseline. Potential differences in CT scan findings	Unclear No No	Yes	Unclear Missing data not described, potential differences in #s used for analyses	Unclear Adherence to HBOT protocol not described	Unclear Not specifically described	Fair
Rockswold 2013[14]	Unclear; Not described Unclear; Not described	Yes	Yes Unclear No	Yes	Yes Exclusion of <5% of patients from analysis	Unclear Adherence to HBOT protocol not described	Yes Intervention group = 5% (1/20) Crossover group= 4.5% (1/22)	Fair

STRENGTH OF EVIDENCE

SOE Grade (High, moderate, low)	Study Design: No. Studies (N)	Study Limitations (High, medium, low)	Directness (Direct or indirect)	Consistency (Consistent, inconsistent, unknown for single study)	Precision (precise or imprecise)	Reporting Bias (Suspected, undetected)	Other Issues (None or describe)	Finding (Results – describe direction in words (greater or lower risk or no difference) and provide data
Mild TBI								
Post-concussion symptom response: Low	1 RCT (72][11]	Medium	Direct	Unknown	Imprecise	Undetected	None	No meaningful differences were detected between the HBOT, sham, or control groups (percent of patients with ≥ 2-point RPQ-3 improvement: 52% vs 33% vs 25%; *P*=0.24)
Quality of life: Low	1 RCT (72)[11]	Medium	Direct	Unknown	Imprecise	Undetected	None	Results favored sham over HBOT group for physical functioning, bodily pain, social functioning, and emotional domains on the SF-36
Ear barotrauma at 1.5 ATA: Low	1 RCT (72)[11]	Medium	Direct	Unknown	Imprecise	Undetected	None	HBOT led to more ear barotrauma compared to sham when given at higher dosages (8% vs 0% at 1.5 ATA for 60 minute sessions)[11]).
Ear barotrauma at 2.4 ATA: Low	1 RCT (50)[15]	Medium	Direct	Unknown	Imprecise	Undetected	None	HBOT led to more ear barotrauma compared to sham when given at higher dosages (42% vs 16%, *P* = 0.57 at 2.4 ATA for

SOE Grade (High, moderate, low)	Study Design: No. Studies (N)	Study Limitations (High, medium, low)	Directness (Direct or indirect)	Consistency (Consistent, inconsistent, unknown for single study)	Precision (precise or imprecise)	Reporting Bias (Suspected, undetected)	Other Issues (None or describe)	Finding (Results – describe direction in words (greater or lower risk or no difference) and provide data
								90 minute sessions)[15]
Moderate to Severe TBI								
Mortality: Moderate	3 RCTs (263) [13,14,16]	Medium	Direct	Consistent	Precise	Undetected	None	HBOT reduced odds of death by 68% (OR 0.32; 95% CI 0.18 to 0.57) compared to control groups[9]
Glasgow Outcome Scale (GOS): Low	3 RCTs (141) [13,14,17]	Medium	Direct	Inconsistent	Imprecise	Undetected	Sensitivity analysis showed the results to be insignificant after the removal of 1 RCT,[13] indicating that the meta-analysis had poor reliability.[9]	HBOT improved GOS by 278% (OR 3.78; 95% CI 1.23 to 11.63) compared to the control groups. However, after removal of 1 RCT,[13] HBOT did not significantly improve GOS (OR 2.18; 95% CI 0.92 to 5.17).[9] The large effect in Ren cannot be explained.
Pulmonary complications: Low	2 RCTs (228)[16,18]	Medium	Direct	Consistent	Imprecise	Undetected	None	HBOT significantly increased risk of severe pulmonary complications (13% vs 0%; RR 15.57; 95% CI, 2.11 to 114.72) compared to control.[7]
Seizures: Low	1 RCT (168)[16]	Medium	Direct	Unknown	Imprecise	Undetected	None	HBOT did not significantly increase seizures

SOE Grade (High, moderate, low)	Study Design: No. Studies (N)	Study Limitations (High, medium, low)	Directness (Direct or indirect)	Consistency (Consistent, inconsistent, unknown for single study)	Precision (precise or imprecise)	Reporting Bias (Suspected, undetected)	Other Issues (None or describe)	Finding (Results – describe direction in words (greater or lower risk or no difference) and provide data
								(2.3% vs 0%; RR 5.0; 95% CI 0.24 to 102.6) compared to control.[7]
Ear barotrauma (Hemotympanum): Low	1 RCT (168)[16]	Medium	Direct	Unknown	Imprecise	Undetected	None	HBOT did not significantly increase hemotympanum (2.3% vs 0%; RR 5.0; 95% CI 0.24 to 102.6) compared to control.[7]

APPENDIX F: RESEARCH IN PROGRESS

Status	Study Title	Study Design	Information Resources (Registry #; citation(s) for published protocols; links to project websites)
Unknown, past anticipated completion date	The effect of hyperbaric oxygen therapy on post-concussion syndrome: a systematic review and meta-analysis	SR	Yan Dong. The effect of hyperbaric oxygen therapy on post-concussion syndrome: a systematic review and meta-analysis. PROSPERO 2016:CRD42016032620 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016032620
Unknown, past anticipated completion date	The effectiveness of hyperbaric oxygen therapy on mortality in adults with craniotrauma: a systematic review	SR	Miloslav Klugar, Ivana Nytra, Sona Bocková, Jitka Klugarová, Zuzana Kelnarová, Jana Marecková. The effectiveness of hyperbaric oxygen therapy on mortality in adults with craniotrauma: a systematic review protocol. PROSPERO 2015:CRD42015016547 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015016547 Published Protocol
Completed, outcome results not yet published	mTBI Mechanisms of Action of HBO2 for Persistent Post-Concussive Symptoms (BIMA)	RCT	U.S. Army Medical Research and Materiel Command NCT01611194
Currently recruiting	Hyperbaric Treatment of Traumatic Brain Injury (TBI)	RCT	Barry Miskin, MD, Jupiter Medical Center NCT01847755
Currently recruiting	Hyperbaric Oxygen Treatment to Treat Mild Traumatic Brain Injury (mTBI)/Persistent Post-Concussion Syndrome (PPCS)	RCT	Paul G. Harch, M.D., Louisiana State University Health Sciences Center in New Orleans NCT02089594
Currently recruiting	Hyperbaric Oxygen Therapy and SPECT Brain Imaging in Traumatic Brain Injury	RCT	Paul G. Harch, M.D., Louisiana State University Health Sciences Center in New Orleans NCT00594503
Currently recruiting	Magnetic resonance imaging study of hyperbaric oxygen treatment on cognitive dysfunction after traumatic brain injury	RCT	Liu Yang, Department of Rehabilitation Medicine, Fuzhou General Hospital of Nanjing Military Command, PLA. Fuzhou, Fujian, China ChiCTR-IOR-16010091
Not yet 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: PEER REVIEW

Comment #	Comment	*Author Response*
Are the objectives, scope, and methods for this review clearly described?		
1.	Yes	*None*
2.	Yes	*None*
3.	Yes	*None*
4.	Yes	*None*
5.	Yes	*None*
6.	Yes	*None*
7.	Yes	*None*
8.	Yes	*None*
Is there any indication of bias in our synthesis of the evidence?		
9.	No	*None*
10.	No	*None*
11.	No	*None*
12.	Yes - I feel the use of special formatting, the phrasing of certain passages, and the uses of certain words; particularly "however" and "despite", convey a subtle bias.	We used “however”, “despite” and italics to draw the general reader’s attention to when something contrasted with what would be commonly expected or previously mentioned. This approach is consistent with common use of these words and formatting in the scientific literature. However, we removed the formatting, both occasions of the word “despite” and all 25 occasions where we used the word “however” in relation to HBOT evidence.
13.	Why is special formatting used on page 1 lines 50-54? To me this adds unnecessary emphasis on the lack of	Removed italics and bolding

	clinically significant symptom improvements in HBOT and thus a bias against its utility	
14.	On page 2 lines 15-32, mild TBI is only discussed in the context of the VA/DoD studies. The Israeli study is not discussed even though it was included in the review as an RCT examining HBOT for mTBI. When discussing HBOT for any condition, exclusion of relevant and quality RCTs done outside the VA implies a bias and is another complaint of HBOT proponents. HBOT proponents complain that the VA staff leading HBOT research studies are personally biased against this treatment, so it is critical to include external to VA research when it is relevant to the topic	The Israeli civilian study by Boussi-Gross 2013 is included in the review (reference #17) and is discussed in detail on page 15, lines 27-50. In the Executive Summary, we highlighted the VA/DoD studies because they are the highest quality and have the greatest relevance to the target Veteran population. We did not mention the Israeli study in the Executive Summary (page 2, lines 15-32) because we were unconvinced of its applicability to Veterans and its overall reliability. Although “acceptable”, It has more methodological limitations than the VA/DoD RCT’s, including a higher potential for nonspecific ‘participation effects’ due to the lack of a sham comparator, inadequate statistical power, and the exclusion from their analysis of twice as many participants from the control group for reasons that could have been related to outcome. However, we have now added to the Executive Summary the following statement: “Although an Israeli civilian RCT had more positive findings, we have more doubt about its reliability due to its greater methodological limitations.”
15.	Similarly, I feel that including a table in the main body of the review of exclusively VA/DoD RCTs implies a certain amount of bias. On page 14 line 23, RCTs in table 2 refer only to VA/DoD studies, this should be explicitly stated or non-VA/DoD RCTs (like the Israeli study) should be included in the Table and the table title should be changed. To be clear, I don't feel that HBOT treatment should be more favorably reviewed in this report. To me, this report seems to have a bias against HBOT when reporting and describing the outcomes of HBOT research. I think edits can be made to help make the review more neutral.	On page 14, line 23, which provides an overview to the Mild TBI section, much like with the Executive Summary, we highlighted the VA/DoD studies because they have the lowest risk of bias and the greatest relevance to the target Veteran population. We added an explicit statement to this regard: “…in the RCTs with the lowest risk of bias and greatest relevance to Veterans, which were conducted by the VA/DoD (Table 2).”
16.	No	*None*
17.	No	*None*
18.	Yes - To a mild degree. This was explained in the attached review with respect to the characterization of the LSU Pilot Trial and its "extreme" results as well as the characterization of its author as an "advocate." Of all of the reviews on this controversial topic this ESP review is	The use of “extreme improvements” was meant to apply to the anecdotal case testimonials of HBOT as a “miracle cure”, not the LSU pilot trial. But, we removed the “extreme improvements” language. We changed all instances of “advocate” to “proponent”. All comments from the “attached review” are now included in this disposition document for reviewer #7.

	one of the least biased and ends with a neutral open-minded recommendation.	
19.	No	*None*
Are there any published or unpublished studies that we may have overlooked?		
20.	No	*None*
21.	No	*None*
22.	No	*None*
23.	No	*None*
24.	No	*None*
25.	Yes - see my response below and uploaded review.	All comments from and our responses to this reviewer's uploaded review have been inserted in this disposition document.
26.	Yes - Please see uploaded review. All of the articles that were not reviewed are those that inform the science that is the basis of the studies. All of them except one are non-RCTs and are mentioned in the attachment. One is a case controlled study whose preliminary data is discussed in the article, but was not published in final version until mid-October 2017; it may not have been available to the authors of the ESP review. The one RCT is the German Holbach study that was referenced in the ESP review, but was likely excluded because the original publication is in German. The ESP review group has an English translation of this article.	All this reviewer's comments from the "uploaded review" are now included in this disposition document. We have added the case-controlled study (Harch 2017) and the German Holbach study, as well as others as detailed below.
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.		
27.	No	*None*
28.	Throughout the document there seems to be some conflating of different conditions (PPCS-mild TIB, PTSD, post deployment syndrome)	We corrected the occasion of PPCS-mild TBI. Otherwise, we noted the post-deployment syndrome terminology in the Introduction just as background and used PPCS only when used by the studies themselves.

29.	Throughout would highly recommend additional effort to break out any discussion/data re: mild/moderate versus severe TBI	Done.
30.	In a system in which resources are limited (VHA), providing a therapy with no evidence-base has implications. This does not seem to be addressed.	We disagree that HBOT has "no evidence-base". For mild and moderate/severe TBI and/or PTSD, all have some evidence, but with remaining uncertainties. We can appreciate this reviewer's point about limited resources. This is a universal issue of particular importance when considering the traditional context of deciding the level of a recommendation for full-scale use of a treatment prior to proven alternatives. However, considerations may be more nuanced when exploring innovative use of new treatment modalities with admittedly emerging evidence bases for small-scale clinical demonstrations in Veterans in whom adequate trials of conventional therapy have been unsuccessful and alternatives are limited – including concepts such as feasibility and general safety.
31.	Executive Summary Would be useful to have an operationalized definition of "failed conventional therapy"? Per the sentence, "However, in the face of failed conventional therapy, when the potential alternative is no care, consideration of offering compassionate HBOT to Veterans with TBI and/or PTSD is reasonable,"… Under what circumstances would there be the alternative of "no care"?	We are not aware of a widely accepted definition of "failed conventional therapy"; thus, we clarified that we mean "when patients do not respond to and/or do not tolerate adequate trials of multiple conventional therapy options". Also, by "no care", we meant no more conventional therapy options. But, we agree with you and reviewer #6 that a better description of the alternative is "consideration of emerging treatment options". Therefore, we've changed the sentence referenced to: "However, when patients do not respond to and/or do not tolerate adequate trials of multiple conventional therapy options and are considering emerging treatment options…"
32.	Executive Summary Based on the evidence – would suggest that providing compassionate HBOT to with TBI and PTSD is not equal. Also mild or moderate/severe TBI? All conditions seem to be treated equally in terms of recommendations. This is confusing as no studies have been completed on PTSD.	Although we agree that the evidence bases of these 3 populations have different types of limitations, we are treating them equally in terms of suggesting that any might be reasonable for a small-scale clinical demonstration as an emerging therapy as they all similarly represent an innovative application of an existing modality that has not yet been fully evaluated and none has a clear signal of serious harm. And while this reviewer is correct that no studies have been completed on exclusively PTSD, several studies have included patients with concomitant mild TBI and PTSD
33.	Executive Summary Unclear how a small pilot would resolve existing questions?	We agree that a small clinical demonstration would not fully resolve existing questions for areas in which we already have imprecise information from RCTs – such as whether the lack of a clinically

		relevant benefit for mild TBI is due to imprecision or generally ineffectiveness. But, a small clinical demonstration could provide preliminary information for areas in which we have no information – such as in a population of exclusively PTSD patients, on comorbidities, clinically relevant patient outcomes, patient expectations, and documentation of the types and durations of previous and ongoing treatments.
34.	Would suggest that additional attention be provided to discussion of the expected course of recovery post-mTBI	We added detail to the Introduction that many people recover with 30 days post-TBI, but that some experience persistent post-concussion symptoms that last longer than 3 months and may take 6 months to a year to completely resolve. We agree this is important context given that the time since most recent TBI occurrence was 8.5 to 60 months post-TBI in the majority of RCTs
35.	"Despite these interventions, a large proportion of patients with PPCS-mild TBI, PTSD and post-deployment…".. many do not receive appropriate evidence-based interventions either for symptoms or conditions. This issue requires additional attention – as well as a review of existing evidence-base (tx) for each of these conditions…	We added to the Introduction that reasons for lack of expected improvement can be complex and multidimensional, including failure to receive evidence-based interventions due to variability in clinician judgment and patients' barriers to access and adherence or presence of confounding prognostic factors, including medical and/or psychiatric comorbidities and/or inadequate psychoeducation. We agree this has important clinical implications and have added this to the "Clinical and Future Research Implications" section: "Because reasons for lack of expected improvement can be complex and multidimensional, including failure to receive evidence-based interventions due to variability in clinician judgment and patients' barriers to access and adherence, to avoid potential further delay of evidence-based treatments, we suggest careful documentation of previous treatments prior to HBOT initiation." We also identified a few recent systematic reviews that confirm that the evidence-base is still limited for VA/DoD CPG-recommended treatments for PCS and PTSD following mild TBI and have add this context to the Introductory paragraph that describes conventional treatment options.
36.	Mechanisms by which HBOT might work are theorized – to the best of my knowledge there is no evidence-base surrounding - this problematic nature of this is not addressed.	There is some evidence on mechanism from animal models of TBI and in TBI patients, which is most recently summarized in a review by Hu et al in 2016. We have refined the text in the Introduction to more clearly note this evidence; "In animal models of TBI, HBOT 1.5 ATA to 3 ATA has increased tissue oxygenation and neuronal stem cell proliferation and reduced inflammation, pressure in the brain and cellular death.(Hu 2016) In TBI patients, HBOT 1.5 ATA to 2.5 ATA

		improved cerebral blood flow(Harch 2012 and Boussi-Gross 2013) and glucose metabolism.(Holbach 1974) Gene array analyses have demonstrated positive impacts on gene expression.(Harch 2015)
37.	How were definitions of clinically significant identified?	As we are not aware of any widely accepted definitions of clinically significant benefit, we noted in the benefits outcomes section of the Eligibility Criteria section that we accepted any definition of clinically significant clinical symptom response - an example of which is the proportion of patients with ≥ 2-point change in Rivermead Post-Concussion Symptoms Questionnaire.
38.	None	*None*
39.	Please change "Community Engagement's (OCE) Center for Compassionate Innovation (CCI)" to Center for Compassionate Innovation (CCI). We are attempting to separate them out as distinct identities to keep things straight.	Changed.
40.	Please change "A small pilot through CCI" to "A small-scale clinical demonstration project through CCI" as it more accurately reflects what we are doing.	Changed.
41.	First and foremost, the purpose of the review that was stated in the SOW should have been identical in the draft of the report. See answer to next question for recommended edits.	Changed to purpose statement from Scope of Work document.
42.	page 2 line 7: HBOT proponents have also raised concerns about personal bias of VA researchers which impacts not only study design but also the interpretation and discussion of HBOT study results.	We added this statement to the Introduction and our rebuttal of the claims to the Discussion: "HBOT proponents have also raised concerns about bias against HBOT in VA/DoD RCT investigators that has led to flaws in the design and interpretation of HBOT research."
43.	pages 4-5: I liked how HBOT treatment was described. This was helpful and will be a good resource in the future to discuss the treatment with those who are unfamiliar with it.	We are happy to hear this description was helpful.
44.	page 6 line 12 - HBOT proponents contend that VA research is biased, which is why they keep going to singular cases or anecdotal evidence as the basis for their argument. Consider rewording this with consideration of the perceived bias in the external to VA community.	Please see our response to similar comment #42 above.

45.	page 6 line 34-35 - the Mayo Clinic article didn't caution against anything, it should not be used as a reference for a warning or caution to consumers	We removed the Mayo Clinic article and reframed our related discussion of the FDA consumer update to more clearly state that it was meant to address internet claims.
46.	Additionally, I think some of the exclusion reasons should be better or more clearly defined, such as "ineligible outcome" or "ineligible systematic review".	Changed PRISMA and supplemental materials to better explain examples of ineligible outcomes (intermediate outcomes) and reasons for exclusion of systematic reviews (outdated or unclear or high risk of bias)
47.	page 3 line 25 - "compassionate HBOT" is not a treatment modality. Describing the treatment or method of delivering the treatment this way doesn't make sense.	We used the word “compassionate” to imply offering emerging treatments that have not yet been fully evaluated but may offer hope. But, we agree this is ambiguous and have removed the word.
48.	page 6 line 51-page 7 line 12 - I don't consider the discussion of float therapy to be relevant to this topic. It certainly isn't an "important consideration for compassionate use of HBOT". Also, compassionate use of HBOT is not a valid description. If this section is not removed, it should be renamed.	The point of discussing float therapy is to inform the general reader that may also be considering a broader scope of emerging treatments that other emerging treatments with similar components exist that may or may not be a better match for their local system context (e.g., access, feasibility). We have been including such context in all of our emerging treatment reviews. We left this information in, but changed the heading of this section to “Considerations for Evaluating Emerging Treatments for TBI/PTSD”.
49.	pages 13 & 16 (tables 1 & 2) - on table 1, reference 17 is included as a good or acceptable RCT. In table 2, four RCTs are listed and they are all VA/DoD studies. Is the Israeli study not counted in table 1 as a good or acceptable quality RCT? Shouldn't table 1 indicate that 5/5 studies were considered good or acceptable quality? Please reconcile this.	The Israeli study is counted in Table 1 an acceptable quality RCT. We inadvertently omitted the Weaver 2016 RCT from table 1. We added it and now Table 1 reflects data from all 4 VA/DoD RCT’s as well as the Israeli RCT.
50.	Throughout document - remove instances of "however" and "despite" such as "despite" on page 6 line 27 and "however" on page 17 lines 32 and 37.	We used “however” and “despite” to draw the general reader’s attention to when something contrasted with what would be commonly expected or previously mentioned. This approach is consistent with common use of these words in the scientific literature. But, we removed both occasions of the word “despite” and all 25 occasions where we used the word “however” in relation to HBOT evidence.
51.	We've (CCI) been in contact with several individuals from the FDA, and we have a letter where they describe their stance on HBOT. They also explained their consumer warning (published in 2013), and I believe the ESP report may have overinterpreted or overstated what they said. Also, it was a consumer report that was published almost	We removed the Mayo Clinic statement and moved and reframed our discussion of the FDA consumer update as being a statement to address anecdotal internet claims.

	5 years ago now. Also, the Mayo Clinic statement was also perhaps overinterpreted.	
52.	I'm unclear the reason some studies were not included and do not see any results or information about animal studies. I understand whey these are not in the "included studies" for the evidence brief, per se, but believe they have considerable utility for understanding the research and future directions.	As noted above, we have added additional detail to better clarify study exclusions coded as 'background', 'ineligible outcome', and 'outdated or ineligible systematic review', both in the PRISMA diagram and in the appendix of excluded studies. We had already noted findings from animal studies based on the Hu 2016 review, but had ambiguously referred to these as "at the cellular level." We have changed this sentence to read, "In animal studies of TBI…"
53.	Page 1, Line 42: "post-deployment syndrome" Includes other symptoms – pain, sensory amplification, medically unexplained symptoms, etc.	Agreed and we provide an expanded definition of post-deployment syndrome in the Introduction on page 5. We had abbreviated the definition for the Executive Summary.
54.	Page 1, Line 49: spell out PCS	Done.
55.	Page 1, Line 55: spell out RCTs	Done
56.	Page 2, Line 10-11 "lack of compelling evidence of effectiveness" – not sure if this is the best way to say this	Changed to "inconclusive evidence"
57.	Page 2, Line 12-13 "we also found that…" – the wording is awkward	Changed this whole sentence to: "Our independent and objective re-analysis of 15 RCTs found inconclusive evidence at least for mild TBI and PTSD and found that current evidence does not clearly support any one argument over another for or against HBOT."
58.	Page 2, Line 15: spell out HOPPS	Done
59.	Page 2, Line 25: spell out O2	Done
60.	Page 2, line 27: spell out VA/DoD	Done
61.	Page 2, Line 28: my preference is to spell out any number less than 10. Please check the document.	Our formatting guidelines follow the American Medical Association style guide which recommends all numbers be stated as numerals except one
62.	Page 2, Line 43-46 "Serious harms of HBOT appear…" this section is awkward	Changed to: "HBOT may increase risk of some serious harms when used in moderate to severe TBI. In patients with moderate to severe TBI, HBOT increased risk of severe pulmonary complications, but not seizures or ear barotrauma compared to sham."
63.	Page 2, Lines 56-69 "However, the evidence of increased…." I was left wondering what makes this	The point of this sentence was to explain that we are unconvinced by the proponents' claims about 1.2 to 1.3 ATA being a mischaracterized

	important – these conditions are also not CMS reimbursable	sham because the documentation the proponents provide are not directly from patients with TBI and/or PTSD, but are from in vitro samples or patients with different conditions whose experiences with 1.2 to 1.3 ATA may or may not be comparable to TBI and/or PTSD, including chronic toxic encephalopathy, autism, cerebrovascular injury, epilepsy, or migraine. We have revised this sentence to better explain this point.
64.	Page 3 Lines 23-24: Not sure "no" care is the alternative. A clinician could try other, also non-EBPs such as mindfulness, non-PTSD specific treatments (e.g., CBT-I, prazosin to help with nightmares, treatment for other co-occurring conditions) recommend "… failed conventional therapy, when potential alternatives are particularly limited, consideration of offering compassionate use of HBOT…"	Per other comments, we changed this to: "When patients do not respond to and/or do not tolerate adequate trials of multiple conventional therapy options and are considering emerging treatment options, offering HBOT to Veterans with mild or moderate/severe TBI and/or PTSD is reasonable."
65.	Page 5, Line 34: why single quotation mark around hypoxia	These were meant to show that the preceding phrase was the definition of hypoxia (a deficiency in the amount of oxygen reaching our tissues). We used this approach in the subsequent paragraph to link the types of HBOT chambers to their definitions (e.g., hard, soft, monoplace, multiplace).
66.	Page 5, line 37: suggest "…. dying, promote new blood vessel growth, regulate cellular metabolism, and promote cellular growth…"	Thank you for your suggestion on how to be more consistent with the verb tenses in this sentence. We changed as suggested.
67.	Page 5, Line 46: double quotation mark around the bends	Changed to single quotation marks.
68.	Page 5, Line 49: "as well as a few additional conditions.." this seems awkwardly stated	We corrected our preceding statement that there are 13 not 15 FDA-cleared indications and removed this sentence about which are endorsed/covered by UHMS and CMS as none are relevant to TBI and PTSD.
69.	Page 5 line 54: suggest "… or urethane ('soft'), or accommodate only one patient ('monoplace') or more than one patient ('multiplace') at a time."	Thank you for your suggestion about how to improve the clarity of this sentence. We changed as suggested.
70.	Page 7, Line 3L "HBOT can be a highly social experience" what makes this statement important for this paper?	The importance of mentioning the social experience is that it is a component of the overall HBOT regimen that may be considered an enhancement over 'usual care' and may have nonspecific 'participation effects' that contribute to HBOT's overall effects.
71.	Page 7, Line 32: consider adding other symptoms of post-deployment multisymptom disorder or post-deployment	Added

	syndrome such as sensory amplification, medically unexplained symptoms, etc.	
72.	Page 7, Line 35: suggest “among those diagnosed with PPCS-mild TBI”	Added the word ‘diagnosed’ to the sentence.
73.	Page 7, line 51: “PPCS-mild TBI, PTSD, and post-deployment syndrome...” are you saying that these are PPCS? This is unclear	No, we removed the dash from PPCS-mild TBI and listed PPCS as a separate entity separated by a comma.
74.	Page 6, Line 6: “other theorized benefits” Need a citation here	Added these citations: 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. Harch PG. Hyperbaric oxygen in chronic traumatic brain injury: oxygen, pressure, and gene therapy. *Medical Gas Research.* 2015;5:9.
75.	Page 17: line 33: “A meta-anlaysis of 2 studies…” Research conducted by Cifu and colleagues demonstrated significant reduction in some PTSD symptoms	We replaced “2 studies” with “the 2 RCTs[21-25] by Cifu et al and Wolf et al that reported…” to clarify in words, in addition to the citations we provided, which 2 RCTs these are.
76.	Page 21, Line 41: see comment on “no care” on page 3	Per comment above, changed “when the potential alternative is no care” to when patients “are considering emerging treatment options”
77.	Appendix D: list of excluded studies: I’m uncertain why some of these studies were excluded – e.g., GAO report, generally those by “background.” And could you help us to understand what made certain studies ineligible?	Further detail was added to the list of excluded studies for why studies labelled as “background” were excluded. These were not studies in the correct population/intervention, but were deemed potentially useful for background or discussion in the report.
78.	The review makes a game attempt at an “independent and objective examination” of the controversial, complicated, and confusing evidence of HBOT in TBI and PTSD.	Thank you.
79.	The review acknowledges that the purported lack of compelling evidence of effectiveness of HBOT for mild TBI and PTSD cannot be fully explained by consistent evidence of ineffectiveness that points to a nonspecific placebo effect.	Yes, but we also state that evidence does not fully support the alternative ‘mischaracterized sham’ explanation. We disagree with both sides of the ongoing debate that the current evidence clearly points to one explanation over another. We simply still don’t know.
80.	Pooling data from HOPPS and the BIMA study would be helpful (but, this is only true if reviewers acknowledge that 1.2 and 1.3 ATA air are doses of hyperbaric oxygen therapy).	We disagree. Both RCTs compared HBOT 1.5 ATA to room air at 1.2 ATA. Adding BIMA data to HOPPS could resolve the question of whether HOPPS’ lack of a significant increase in proportion of patients with a clinically relevant improvement was due to imprecision or inefficacy. This would be informative regardless of how the 1.2 ATA condition is interpreted – sham or a lower dose of HBOT.

81.	One of the review's conclusions is sound: "In the face of failed conventional therapy… when the potential alternative is no care, it is reasonable to offer compassionate HBOT to Veterans with TBI and/or PTSD…"	Noted. We stand by our other conclusions as well: In summary, the large treatment benefits demonstrated for HBOT in uncontrolled case series have not been easily replicated in well-controlled RCTs. Potential explanations for this include that the potential benefits are subtle and demonstration requires larger RCTs, HBOT is in fact ineffective, or the sham design has indeed been problematic. We disagree with both sides of the ongoing debate that the current evidence clearly points to one explanation over another. We simply still don't know. Pooling data from the HOPPS trial and the yet unpublished BIMA trial – both of which compared HBOT 1.5 ATA to room air at 1.2 ATA, and used the RPQ to measure PCS symptoms – could shed light on the debate. Broad usage of HBOT as an initial treatment for TBI and/or PTSD in lieu of conventional treatments still does not appear warranted.
82.	The review's acknowledgement that a viable option for HBOT is the Medicare-like Coverage with Evidence Development pathway for Veterans in whom other treatments have not been successful seems reasonable.	Noted.
83.	Failure to understand the science and scientific definition of HBOT with respect to hydrostatic pressure and hyperoxia, the bioactivity of both, and the nature of hyperbaric oxygen therapy as a drug whose effects are dependent on dose.[1-5] 1. Harch PG. HBO therapy in global cerebral ischemia/anoxia and coma, Chapter 20. In Textbook of Hyperbaric Medicine 6th ed. , K.K. Jain, ed. Springer, Cham, Switzerland. 2017, pp. 269-319. 2. Harch P. Department of Defense trials for hyperbaric oxygen and TBI: Issues of study design and questionable conclusions. Undersea Hyper Med. 2013;40:469-70. 3. Figueroa XA, Wright JK. Hyperbaric oxygen: B-level evidence in mild traumatic brain injury clinical trials. Neurology. 2016:87:1-7. 4. Harch PG. Hyperbaric Oxygen Therapy for Post-Concussion Syndrome: Contradictory Conclusions from a Study Mischaracterized as Sham-Controlled. J Neurotrauma. 2013;30:1995-1999.	We disagree that we fail to understand the science and scientific definition of HBOT, which we have described as "a combination treatment of increased oxygen (hyperoxia) at increased hydrostatic pressure", which is consistent with your comment here. We have discussed in detail the mischaracterized sham argument which states that the low pressure of 1.2 to 1.3 ATA HBOT used in the sham control groups to mimic HBOT at higher pressures is not inactive in the traditional sense of an inert placebo, but has therapeutic benefits. Although we have reviewed all of and cited some of the 5 citations listed here, we remain unconvinced because none directly demonstrate clinical benefits specifically in TBI patients.

	5. Harch PG. Hyperbaric oxygen in chronic traumatic brain injury: oxygen, pressure, and gene therapy. Med Gas Res. 2015;5:9. doi: 10.1186/s13618-015-0030-6	
84.	Page 2, line 13; Page 21, line 31: The authors repetitively state that both proponents and opponents in the HBOT/TBI, PTSD debate misconstrue the evidence. It is not clear how the proponents have misconstrued the evidence after reviewing the proponents' arguments in multiple publications, a number of which were not included in the review, but are supplied below.[3,5,6] 3. Figueroa XA, Wright JK. Hyperbaric oxygen: B-level evidence in mild traumatic brain injury clinical trials. Neurology. 2016:87:1-7. 5. Harch PG. Hyperbaric oxygen in chronic traumatic brain injury: oxygen, pressure, and gene therapy. Med Gas Res. 2015;5:9. doi: 10.1186/s13618-015-0030-6. 6. Efrati S, Ben-Jacob E. Reflections on the neurotherapeutic effects of hyperbaric oxygen. Experta Rev Neurother, 2014;14(3):233-236.	We have removed reference to anyone misconstruing evidence. We reframed this to better reflect our position that we are unconvinced that the current evidence clearly points to one explanation over another for why well-controlled RCT's have not easily replicated the large treatment benefits demonstrated for HBOT in uncontrolled case series. The type of evidence that would be most convincing of the mischaracterized sham argument – that low-pressure HBOT of 1.2 to 1.3 ATA is potentially bioactive – is bioactivity evidence specifically in patients with TBI and/or PTSD. None of these 3 studies here provide such evidence.
85.	Omitting a relevant article that is not an RCT or ignoring relevant data from an RCT article that significantly inform the review.[7,8] This refers to the functional imaging data, the only imaging data that is available on this HBOT-treated subject population. See discussion below. 7. Harch PG, Andrews SR, Fogarty EF, Amen D, Pezzullo JC, Lucarini J, 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;29:168-185. 8. Boussi-Gross R, Golan H, Fishlev G, Bechor Y, Volkov O, Bergan J, et al. Hyperbaric Oxygen Therapy Can Improve Post Concussion syndrome Years after Mild Traumatic Brain Injury-Randomized Prospective Trial. PLOS ONE. 2013;8:1-18.	We added these studies to the Introduction as evidence of the physiological effects of HBOT specific to TBI as you suggested in your comment #89 below.
86.	Multiple places in the manuscript: Continuing to call the 1.2 and 1.3 ATA hyperbaric treatment groups "sham"	We added clarification to the report that our use of the word 'sham' in no way reflects any position of whether or not this is a

	groups and grouping them with no treatment control groups or comparing them as a control group to the 100% oxygen groups. They are different doses of hyperbaric oxygen therapy as has been argued in multiple peer-reviewed publications[2-6,9] and not refuted in any scientific publication. This issue was addressed by the same reviewer group's director in the Agency for Healthcare Research and Quality review of HBOT for Brain Injury, Cerebral Palsy, and Stroke.[10] The authors of that review concluded on page 44 that "The possibility that pressurized room air had a beneficial effect on motor function should be considered the leading explanation" for the equivalent improvements in Gross Motor Functional Measures in the oxygen and air groups. In the present ESP review the authors have dismissed this previous conclusion as having not been proven in mild TBI (Page 2, lines 56-60). See #7 below 2. Harch P. Department of Defense trials for hyperbaric oxygen and TBI: Issues of study design and questionable conclusions. Undersea Hyper Med. 2013;40:469-70. 3. Figueroa XA, Wright JK. Hyperbaric oxygen: B-level evidence in mild traumatic brain injury clinical trials. Neurology. 2016:87:1-7. 4. Harch PG. Hyperbaric Oxygen Therapy for Post-Concussion Syndrome: Contradictory Conclusions from a Study Mischaracterized as Sham-Controlled. J Neurotrauma. 2013;30:1995-1999. 5. Harch PG. Hyperbaric oxygen in chronic traumatic brain injury: oxygen, pressure, and gene therapy. Med Gas Res. 2015;5:9. doi: 10.1186/s13618-015-0030-6. 6. Efrati S, Ben-Jacob E. Reflections on the neurotherapeutic effects of hyperbaric oxygen. Experta Rev Neurother, 2014;14(3):233-236. 9. 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. Med Gas Res. 2017;7(3):156-174.	mischaracterization. Regardless of the debate over whether or not the comparator groups of room air at < 1.5 ATA have been mischaracterized as 'sham' and are actually a therapeutic dose of HBOT (described above), for the sake of describing the included study results, we will refer to them as sham. As for the 2004 AHRQ report on HBOT for CP, this reviewer is correct that (1) our group's director contributed to that 2004 report that concluded that therapeutic effects of pressurized room air should be considered the leading explanation for equivalent improvements in Gross Motor Functional Measures in the oxygen and air groups and (2) that conclusion is inconsistent with this groups conclusion about pressurized air for TBI. The reason for the difference is the variation between populations in the plausibility of the 'participation effects'. In the case of CP, as stated below, the 'participation effect' argument is less convincing because there was "no evidence to suggest that the parents and their children had less time together, or less stimulating interaction, before the study began." So, there was less of a need to rule out the participation effect with physiologic data. But, for TBI, the 'participation effect' seems more plausible - active service members were temporarily reassigned for study participation, often with greatly reduced duty schedules and enhanced access to leisure time and activities – sometimes in a noncombat, semitropical beach environment; and got to participate in a "high-tech, high-touch" daily "ritual" involving daily interactions with a team of nurses and hyperbaric technicians, as well as interactions with other participants in multiplace chambers. So, because of plausibility of participation effects for adults with TBI/PTSD, there is a greater need to rule them out with direct evidence of physiological/biological effects specifically in TBI patients.

87.	Failure to compare HBOT outcomes in a comparative effectiveness analysis to other treatments. The authors base effectiveness conclusions on "clinically significant" outcome changes which were only defined for the RPQ-3. It would inform the discussion on the magnitude of the HBOT treatment effects if they were compared to standard of care treatment of PPCS and PTSD. The magnitude of purported placebo effects can then be compared.	We did not compare HBOT to other standard of care treatments because we did not identify any studies that directly compared HBOT to any specific "standard of care treatment", such as cognitive rehabilitation. We did not attempt to substitute indirect comparisons between the HBOT evidence and a separate body of evidence on any "standard of care treatment" alternatives because we anticipated that interpretation of such indirect comparisons would be seriously limited by heterogeneity between bodies of evidence from the same sources as was the case even between the VA/DoD HBOT studies: outcome assessment methods, timing (immediately following therapy, up to 6 weeks after discontinuation), and patient populations (time since most recent TBI, baseline symptom severity, number of previous TBI's, medical and psychiatric comorbidities, etc.)
88.	Failure to acknowledge the central flaw in the Cifu, et al and Miller, et al14 arguments of ritual/placebo explanation of positive treatment group results in theirs and other researcher's studies,[7,8] namely, the disparity in results between their own studies. Analysis of the data reveals that the "sham" groups in Wolf, et al and Miller, et al both performed better than the "sham" and two other treatment groups in the Cifu, et al study. If ritual/placebo were responsible for the positive results in Wolf, et al and Miller, et al they should have been present to a greater degree in the Cifu, et al which took place in beautiful Pensacola, Florida.5,9 The opposite occurred where Cifu, et al had the least positive (2.0 ATA group for PCL-M outcome only) and most neutral results of all studies. The disparity in results between the studies is better explained by the different effects of different doses of hyperbaric therapy.[5,9] 5. Harch PG. Hyperbaric oxygen in chronic traumatic brain injury: oxygen, pressure, and gene therapy. Med Gas Res. 2015;5:9. doi: 10.1186/s13618-015-0030-6. 7. Harch PG, Andrews SR, Fogarty EF, Amen D, Pezzullo JC, Lucarini J, 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;29:168-185.	We appreciate the logic that the Cifu results seem contradictory to what one would expect considering sham ATA levels alone (2.0 in Cifu and 1.2-1.3 in Wolf and Miller). But, we cannot conclude that sham pressure alone is responsible for this inconsistency when there were so many other sources of heterogeneity between those studies: in the air delivered (10.5% O2 vs room air, outcome assessment methods, timing (immediately following therapy, up to 6 weeks after discontinuation), and patient populations (most recent TBI ranged from 3 to 71 months). This heterogeneity in so many factors across the VA/DoD studies is the primary reason we found their interpretation to be difficult. The type of evidence that would be most convincing of the mischaracterized sham argument – that low-pressure HBOT of 1.2 to 1.3 ATA is potentially bioactive – is bioactivity evidence specifically in patients with TBI and/or PTSD. None of these studies cited here provide such evidence.

	8. Boussi-Gross R, Golan H, Fishlev G, Bechor Y, Volkov O, Bergan J, et al. Hyperbaric Oxygen Therapy Can Improve Post Concussion syndrome Years after Mild Traumatic Brain Injury-Randomized Prospective Trial. PLOS ONE. 2013;8:1-18. 9. 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. Med Gas Res. 2017;7(3):156-174.	
89.	#7 The reviewers acknowledge that HBOT is a treatment for a variety of "injury" conditions as documented in the UHMS, CMS, and FDA lists (Appendix A). They also acknowledge that HBOT is purportedly treating the microscopic and macroscopic wounds of TBI (Page 1, lines 31-33), thereby including TBI in the "injury" conditions for which HBOT may be effective. Essentially, HBOT is non-specifically treating all of these injury/wounding conditions. However, when they cite the multiple episodes where 1.3 ATA compressed air has been shown/purported to have positive benefits on blood flow in chronic central nervous system disorders (Page 2, lines 56-60) they contradict this logic by stating that the same has not been shown specifically for 1.3 ATA in TBI, excluding it as a separate and distinct wounding/injury condition. While technically correct this is inconsistent reasoning and inconsistent with the non-specific effects of hyperbaric therapy on gene expression/suppression and disease pathophysiology.[1,2,4,5] This inconsistency should be corrected. 1. Harch PG. HBO therapy in global cerebral ischemia/anoxia and coma, Chapter 20. In Textbook of Hyperbaric Medicine 6th ed. , K.K. Jain, ed. Springer, Cham, Switzerland. 2017, pp. 269-319. 2. Harch P. Department of Defense trials for hyperbaric oxygen and TBI: Issues of study design and questionable conclusions. Undersea Hyper Med. 2013;40:469-70. 4. Harch PG. Hyperbaric Oxygen Therapy for Post-Concussion Syndrome: Contradictory Conclusions from a	Thank you for identifying the potential inconsistency in our reasoning. We have corrected this by refining our discussion of the mechanisms of HBOT's effects at 1.5 to 3 ATA in TBI by citing physiological data from animal and human studies specifically in TBI. In addition to the theory of the non-specific effects of HBOT, it is ideal to directly demonstrate them in the specific populations of interest. Adding information about the physiologic data for HBOT1.5 to 3 ATA specifically in TBI strengthens our point of the lack thereof for lower pressure HBOT at 1.2 to 1.3 ATA, where there are no data in TBI.

	Study Mischaracterized as Sham-Controlled. J Neurotrauma. 2013;30:1995-1999. 5. Harch PG. Hyperbaric oxygen in chronic traumatic brain injury: oxygen, pressure, and gene therapy. Med Gas Res. 2015;5:9. doi: 10.1186/s13618-015-0030-6.	
90.	The reviewers repetitively refer to proponents of HBOT for TBI and PTSD as both proponents and "advocates" (Page 6, line 11; Page 14, line 50; Page 19, line 19; Page 20, line 50; Page 21, line 24: and discuss the proponents' position in the setting of the "extreme" results of the LSU Pilot Trial and the statement about a no-chamber group "which an HBOT advocate" described as the "only acceptable control group". The term "advocate" is derogatory and disparaging from a scientific standpoint and should be eliminated. It minimizes the scientific argument lodged by the proponents in multiple peer-reviewed scientific journals. The characterization of the no chamber group as the "only acceptable control group" should be explained by the authors. As the author of that statement explained in a simultaneous publication4 it was the only control group which lacked the bioactive components of hyperbaric therapy, pressure and hyperoxia. It specifically addressed the obstacles to performing a hyperbaric study that controlled for the bioactivity of hydrostatic pressure. To do such a pressure control group one has to eliminate adiabatic heating and pressure-volume effects on the middle ear. No study has yet been performed that has eliminated these two components. As explained, to do so would require placing pressure equalization tubes in the ears of all subjects and having a climate controlled chamber. PETs for all study participants is an unreasonable burden on subjects and has not been done in a study that this reviewer is aware of. A climate-controlled system is available for chambers, but has not been used in any study. There is a distinction between researchers and clinicians who are making these types of arguments and true advocates such as Congressman Jones and other lawmakers who have enacted laws to advance hyperbaric	We did not mean any disrespect and have changed "advocate" to "proponent". To the occasions of "only acceptable control group", we added: "which an HBOT proponent described as the "only acceptable control group" (52% vs 33% vs 25%; *P*=0.24) because it lacks the potentially bioactive components of pressure and hyperoxia."

	oxygen therapy for veterans. The word "advocate" should be eliminated.	
91.	The authors made a significant error in their reading of the results of the HOPPS trial.14 (Page 14, line 50; Page 19, line 20). This misread of the RPQ data negates a component of their assertion that the proponents misconstrued the evidence regarding effectiveness of HBOT in TBI and PTSD. The RPQ outcome in the air ("sham") and 1.5 ATA oxygen groups were not compared to the no-chamber group. This was only done in the Israeli Civilian RCT.[8] See discussion below. 8. Boussi-Gross R, Golan H, Fishlev G, Bechor Y, Volkov O, Bergan J, et al. Hyperbaric Oxygen Therapy Can Improve Post Concussion syndrome Years after Mild Traumatic Brain Injury-Randomized Prospective Trial. PLOS ONE. 2013;8:1-18.	We consulted with an independent and external biostatistician who confirmed our reading of the RPQ data in Miller 2015: "No differences were observed between groups for improvement of at least 2 points on the RPQ-3 subscale (25% in the no intervention group, 52% in the HBO group, and 33% in the sham group; *P*=0.24)." This biostatistician stated that this finding reflects "an overall test to see whether there is any difference among the three groups," which confirms that the sham and 1.5 ATA groups were compared to the no-chamber group.
92.	The authors mention the importance of clinically meaningful outcomes (Page 1, lines 53-56; Page 3, lines 27-29; Page 7, lines 17-18; page 20, lines 38-42; page 20, lines 55-58; page 21, line 18) in the present reviewed studies and future studies, but offer no suggestions for the best outcomes to use. In a broad sense this is a criticism of most reviews and meta-analyses. This reviewer would recommend that the authors make some suggestions for best outcome instruments for this subject population. It could contribute significantly to future VA research on these topics.	Great suggestion. However, we are not aware of validated outcome measures for interventional trials in PCS or PTSD. We added this the Future Research section: To improve our knowledge about HBOT's potential to improve clinically meaningful outcomes, we suggest establishment of a set of validated outcome measures including minimally important symptom difference thresholds.
93.	The moderate to severe TBI review is limited and flawed. The details are explained below. The study also excluded foreign language literature, especially the work of Holbach and his RCT which is reference #53. That RCT showed a significant reduction in mortality and improvement in outcome and would contribute to the overall conclusions. In the interest of the science and impact on recommendations it should be included.	Please see our detailed response to comment #96 below regarding how we have refined our speculation that seizure risk may be higher in TBI than in other populations to "Therefore, the magnitude of seizure risk in patients with TBI and/or PTSD remains uncertain due to imprecision and inconsistency." Although we concluded that HBOT may reduce mortality in moderate to severe TBI, consistent with this reviewer's point, this reviewer is also correct that our synthesis of mortality for moderate to severe TBI focused on the newest SR, which did not include the Holbach 1974 RCT (reference #53). We have updated this section to also mention findings from the Bennett 2012 SR meta-analysis that does include

		Holbach 1974. This did not change our conclusions. But we will also note that in patients with moderate to severe TBI, to best demonstrate a clinically important benefit over usual care, ideally (1) HBOT would significantly reduce risk of mortality and (2) improve the functional status and quality of life of the survivors, and (3) these benefits could be attributed specifically to HBOT and not between-group differences in the intensity level of medical care and decisions about life-sustaining treatment. We still conclude that the presence of a mortality reduction alone is insufficient to broadly conclude a clinically important benefit for HBOT.
94.	The PTSD review suffers from the same problems as the mild TBI review above with the mis-characterization of the sham groups as control groups when they are in fact different doses of hyperbaric therapy. This dose argument was most recently reviewed in the completed LSU Pilot Trial publication in Medical Gas Research, 10/2017.[9] 9. 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. Med Gas Res. 2017;7(3):156-174.	We have described the dose argument in the Introduction and Discussion of this report and cited this Harch 2017 publication. Regardless of the debate over whether or not the comparator groups of room air at < 1.5 ATA have been mischaracterized as 'sham' and are actually a therapeutic dose of HBOT (described above), for the sake of describing the included study results, we will refer to them as sham and have added this text to our methods section to clarify this.
95.	In Section KQ2 page 18 last paragraph it is stated, "In contrast, rates of inner ear barotrauma for HBOT in RCTs of mild TBI were somewhat higher at 8% to 42%." This is misstated; it should be middle ear barotrauma. True inner ear barotrauma is rare in clinical hyperbaric medicine and if recorded at 8-42% rates would preclude future studies.	We confirmed that the 8% is inner ear barotrauma from Miller 2015 eTable: 2/24=8.3%. We agree that the 42% is an error, though. The Crawford 2017 systematic review reported 10 cases of "ear barotrauma" from Wolf 2012. But, Wolf 2012's side effects publication reported ear barotrauma as 5.91%. We have changed to this: "In contrast, rates of 8% for inner ear barotrauma and 5.91% for ear barotrauma for HBOT in RCTs of mild TBI were somewhat higher"
96.	Also in KQ2, page 18, same paragraph, the statement on seizure risk is misleading. The rate in moderate to severe TBI of 2.3% is from the Rockswold study where the great majority of the patients were a select group of patients: severe TBI patients on ventilators, average GCS of 6.2. It is an unfair comparison to a clinical hyperbaric treatment program that includes the entire spectrum of HBOT patients which are mostly stable outpatients. A better comparison would be to critically ill carbon monoxide poisoned patients where the seizure frequency is similar	We agree this is potentially an unfair comparison based on baseline seizure risk, which is likely higher in Rockswold. We have added this context and removed the speculation that this implies a generally greater susceptibility to seizure risk with HBOT in people with TBI. Thank you for providing the Hampson 1996 reference. We added it and refined the text as below. But, we don't think it is necessarily a "better comparison" because the HBOT doses are higher (2.45 to 3.0 ATA) and its findings are mixed. At the highest HBOT doses (2.80 to 3.00 ATA), which are higher than in Rockswold, yes, the seizure risk is similar, which supports your suggesting that it may be the greater

	to the TBI patients and can be as high as 3%, depending on the dose of HBOT.[16] 16. Hampson, NB, Simonson SG, Kramer CC, Piantadosi CA. Central nervous system oxygen toxicity during hyperbaric treatment of patients with carbon monoxide poisoning. Undersea and Hyperbaric Medicine, 1996;23(4):215-219.	baseline illness severity that is elevating the seizure incidence in Rockswold. But, then Hampson's finding that seizure risk was 0.3% at 2.45 ATA, refutes this logic. It is unclear. Changed text to: "HBOT 1.5 ATA to 2.4 ATA was associated with a 0.3% rate of seizures based on the most recent and one of the largest retrospective cohorts of 2,334 patients treated for a wide variety of conditions at the Sagol Center of Hyperbaric Medicine and Research in Israel between June 2010 to December 2014.[26] In patients with moderate to severe TBI, rates of seizures were higher for HBOT 1.5 ATA. (2.3%)[16] Although, this may reflect a greater baseline seizure risk in patients with moderate to severe TBI compared to the likely stable outpatient status of the study by Hardanny et. al.,[26] this is still higher than in the critically ill carbon monoxide poisoned patients who were treated with higher pressures of 2.45 ATA (0.3%) and 3.0 ATA (2.0%), but not those at 2.80 ATA (3.0%).(Hampson 1996) Therefore, the magnitude of seizure risk in patients with TBI and/or PTSD remains uncertain due to imprecision and inconsistency."
97.	Executive Summary Line 6: I think it is a misleading misconception to say "(HBOT) is designed to increase the supply of oxygen to our blood and tissues." Yes, some of the reasons we use HBO is to do just this, but there is a lot more to HBOT than simply 'increasing oxygen supply'. Oxygen is a drug and at the high doses we administer with HBOT, it has a plethora of interesting pharmacological effects, some of which we can utilize for health benefits. It is not all about reversing hypoxia.	Per the Bennett 2012 Cochrane Review and Hu 2016, expanded this to: "Hyperbaric oxygen therapy (HBOT) is designed to increase the supply of oxygen to our blood and tissues and also thought to have osmotic and angiogenesis effects."
98.	Page 4, Lines 25-30: These calculations ignore water vapour (47mmHg) and CO2 (45 mmHg) in the alveolus, thus the figure of 1064 mmHg is incorrect in terms of the PO2 to which the pulmonary capillaries are exposed.	We intended these calculations of oxygen partial pressure as a way to emphasize the magnitude of the enhanced conditions in a single parameter. But, because they are not key to interpretation of the evidence, we have deleted them.
99.	Page 4, Lines 33 to 38: I think this argument is not sufficient to properly explain what might be going on with HBOT. Yes, injured tissue may not be receiving sufficient oxygen to maximise healing, but this cannot be the mechanism invoked for all the potentially beneficial effects of HBO in the clinical situation. For example, your first suggestion concerning 'fuel for the necessary healing	As in Executive Summary, as noted above, per the Bennett 2012 Cochrane Review and Hu 2016, expanded this to: "Hyperbaric oxygen therapy (HBOT) is designed to increase the supply of oxygen to our blood and tissues and also thought to have osmotic and angiogenesis effects."

	processes' is stem cell production. Surely you are not suggesting the bone marrow has been injured and is hypoxic? Here is a clear piece of evidence that high oxygen partial pressures in the arterial blood lead to the release of vasculogenic stem cells – almost certainly through a nitric oxide mediated pathway. This has absolutely nothing to do with hypoxia, traumatised tissue, impaired blood flow etc.	
100.	Page 4, Line 47: See my notes on Appendix A.	As detailed below, we have corrected Appendix A to only reflect a list of the 13 FDA-cleared indications. We deleted the UHMS endorsements and CMS coverages because none include TBI or PTSD and are not really relevant to this report.
101.	Page 4, Line 58: I am not sure of the relevance of reference 5 for this statement about requiring a specially trained technician operating under physician supervision. The sof chambers referred to are often marketed as being useable by a non-expert and certainly a non-physician. I absolutely agree HBOT should be delivered by properly qualified technicians and physicians, but sadly this is not always so.	This statement came from the following quote from reference #5 (Linda 2015): "Hyperbaric intensive care should be performed within a hospital and be supervised by properly trained and experienced medical staff with intensive care skills", as well as from HBOT websites such as this: https://www.rehabmart.com/post/ultimate-guide-to-hyperbaric-oxygen-therapy. We included the statement to provide context about the potential resources needed to help consider feasibility. But we have softened the language by changing "required" to "are ideally operated by..".
102.	Page 5, Lines 24 to 36: This is a nice summary of TBI and PTSD, I wonder if a short couple of sentences on what might cause PTSD in those with no history of physical head trauma. Are we hypothesising two distinctly different causes of the same syndrome, or are there two different subtypes of PTSD corresponding to trauma and no-trauma cases? This is an important criticism of the use of HBOT in this area being directly related to the TBI/concussion episode rather than hypothesising it is a treatment for PTSD	Added: In those with no history of physical head trauma, exposure to a life-threatening event or traumatic emotional experience can lead to abnormal activation of certain brain regions, such as the amygdala, which may also be involved in the development of PTSD. Discussion exists about the relationship between PTSD and TBI, whether PTSD-like symptoms in TBI should be classified as PTSD or a TBI symptom(Eve 2016) or whether PTSD with and without a history of physical head trauma may have different mechanisms and/or should be classified as different subtypes(Appendix G – peer review disposition document).
103.	Page 13, Line 11: The use of 'only' here in relation to the proportion of participants with PTSD seems a bit pejorative – I recommend simply quoting this range without any qualifications. After all, as you suggest, these studies were not of PTSD per se, so the implication they somehow 'only' enrolled so many sounds like a complaint about the quality of the studies.	Deleted the word "only" as suggested.

104.	Page 13, Line 22: I am not sure what an 'HBOT manufacturer' is. ?Hyperbaric oxygen chamber manufacturer? Why would you seek academic papers from a group of industrial manufacturers rather than consult leaders in the field of hyperbaric medicine or the authors of included studies?	Yes, we meant HBOT chamber industry manufacturer. We added the word "chamber" to clarify this. The practice of soliciting scientific information from industry manufacturers is standard across many US evidence synthesis programs and has resulted in identification of important data on pharmacological treatments. We supplement this process by consulting leaders such as yourself through this peer review process.
105.	Table 1. I note the quality column and the note that suggests you used the Cochrane Collaboration's risk tool. I am guessing you mean the Risk of Bias Tables for individual studies. This is not a measure of quality, but of exactly what it says (Risk of Bias). Also, you would need to tell us how you defined the stratification levels you quote here (what exactly constitutes 'acceptable' quality or RoB here?). In my experience, the term quality in reviews such as this is about the quality of evidence, not the quality of each individual study.	For quality/risk of bias in RCT's, we accepted the ratings previously performed by the Wang 2016 and Crawford 2017 systematic reviews. Wang et al used the Cochrane Risk of Bias Tool and Crawford et al used the Scottish Intercollegiate Guidelines Network Checklist for RCTs. We confirmed general concordance with their ratings by performing a pilot test of 4 RCTs. To better clarify the information in the "Quality" column of Table 1, we have changed the column heading to "methodological limitations" and revised the entries to 'few' (good quality/low risk of bias), 'some to numerous' (unclear risk of bias/ acceptable quality), 'unacceptable' (high risk of bias/poor quality).
106.	Page 14, Line 30 to 32: I understand your thoughts here, but could one not also posit that the similarity of apparent effects across a range of HBOT protocols indicates that there is no sign of any dose-response relationship – mitigating against the likelihood of a pharmacological effect? Similarly, there is no sign of a differential effectiveness dependent upon how you measure the outcome.	Because there are so many sources of heterogeneity, in HBOT and sham protocol, outcome assessment method and timing, and patient populations (most recent TBI ranged from 3 to 71 months), setting, previous and concomitant treatments, we disagree that we can draw conclusions based on isolating just one source of heterogeneity.
107.	Page 14, Line 40: Why have you put 'sham' here in quotation marks? You have already cast doubt on the fact that these really were sham by saying they were characterised as sham – so it is clear you are giving some credence to the argument these are not sham treatments. There is no need for the extra emphasis – it only serves to suggest you have already made your minds up. As to this argument about the sham exposures, clearly in one sense they are certainly sham exposures – they are designed (and successfully) to mimic (sham) a real HBO treatment session. Further, I am personally unimpressed by the arguments that all these different sham procedures must be serendipitously equally effective as each of the HBOT schedules to which they	We have not made our minds up about sham and had actually used the quotes to indicate that questions remain about whether sham has been mischaracterized. We have removed the quotes and acknowledge we are using the word sham in the basic sense that you described – that they were designed to mimic HBOT. We agree that "none of these exposure is actually effective" is one possibility and have said as much in the report:" Potential explanations for this include that the potential benefits are subtle and demonstration requires larger RCTs, HBOT is in fact ineffective, or the sham design has indeed been problematic." But, at the point we don't think that the current evidence clearly points to one explanation over another. We simply still don't know.

	were compared. This seems unlikely – except in the circumstance that none of these exposures is actually effective. The arguments that these relatively trivial exposures are effective treatments (or at least as effective as 'real' HBOT) are very poorly grounded in any scientific evidence – most arguments put forward cite evidence about real HBOT rather than mild air breathing with PO2s easily achievable without compression. I certainly agree with your remarks about power, short term outcomes and clinically inconsequential improvements.	
108.	Page 18, Lines 22-23: Are you sure these are rates for inner ear barotrauma – sounds very high to me (and more like middle ear barotrauma figures).	We confirmed that the 8% is inner ear barotrauma from Miller 2015 eTable: 2/24=8.3%. We agree that the 42% is an error, though. The Crawford 2017 systematic review reported 10 cases of "ear barotrauma" from Wolf 2012. But, Wolf 2012's side effects publication reported ear barotrauma as 5.91%. We have changed to this: "In contrast, rates of 8% for inner ear barotrauma and 5.91% for ear barotrauma for HBOT in RCTs of mild TBI were somewhat higher"
109.	Page 19, Line 11: I think you need to tell the reader about how the evidence is miscontgrstrued by each side in the argument. It is not at all clear where this statement comes from in the sections that precede it. I think a summary is needed here	Per previous comments, we have removed suggestion that anyone has misconstrued the evidence and reframed the Summary and Discussion to focus on our perspective that RCTs have not easily demonstrated large treatment benefits and are unconvinced by any one explanation over another. Then, we proceed to summarize the benefit and harm evidence and the limitations of the explanatory arguments (heterogeneity and indirectness).
110.	Page 19, Line 19-20: There are a few lines here that seem to be an exact repeat of those at the bottom of page 14.	Yes, you are correct. We have refined the text here to be a more concise summary of the text from the Results section on page 14.
111.	Page 19, Line 52 – 55: Also, these changes could be the result of a placebo effect or participation effect directly…	Added.
112.	Page 19, Line 58: I accept your argument here, but I am not sure the sense of equivalence between the two opposing views is an appropriate one. I think it may be worth considering adding something to the effect that it is not reasonable (and indeed in principle not possible) to be required to prove a negative – it is incumbent on those who maintain that HBOT is an effective treatment for these patients to do so. Prudence suggests we should not institute routine use of a therapy until there is a reasonable level of evidence to back up the net benefit of doing so.	Added: "We are not suggesting that it is incumbent on the skeptics to prove ineffectiveness. We are only noting the limitations that preclude clear interpretation of the VA/DoD RCTs as demonstrating consistent evidence of no effect."

113.	Page 20, line 48: Exactly what would constitute 'consistent evidence of ineffectiveness' when there is not a single RCT of the four studying mild-TBI patients that suggests HBOT is more effective than sham?	As we have outlined in the 'Clinical and Future Research Implications' section of the report, a great opportunity to evaluate consistency in effects across studies is between HOPPS and the yet unpublished BIMA. They used identical comparison groups of HBOT 1.5 ATA and room air 1.3 ATA and assessment tools and had similar military populations. Because there is heterogeneity in so many factors across HOPPS and Cifu 2014 and Wolf 2012, we feel it is impossible to conclude that it is the HBOT ineffectiveness that is the single factor driving the findings across studies and not other factors, such as whether HBOT effects vary by time since most recent TBI (8.5 months in Cifu and 23 months in Miller), % with PTSD (higher in Miller), etc.
114.	Page 21, Line 49 and on: In my opinion, such a plan is very likely to end up with a whole lot of data showing some improvements with HBOT that may have nothing to do with true pharmacological effects and everything to do with placebo and participation effects. At least the whole scheme should be run with cheap devices that deliver air at 1.3 ATA or so and probably do no harm and do not need medical specialists to be in attendance. The recommendation about improved RCTs are sound except I do not understand the point of a 'no treatment' arm that research to date would suggest will see no benefit. You are absolutely correct that any future trials should have the control designed with the participation of HBOT proponents – future triallists must be satisfied the sham therapy is both inactive and convincing. This will be a difficult task	Small-scale clinical demonstration with evidence development: Because the effects of HBOT remain unclear, we cannot rule out the possibility that any benefits of a small-scale clinical demonstration project would be due to participation effects. But, for patients who do not respond to and/or do not tolerate adequate trials of multiple conventional therapy options and are considering emerging treatment options, offering a small-scale demonstration of HBOT to Veterans with mild or moderate to severe TBI and/or PTSD seems reasonable. No treatment arm: First, we updated this to "wait-list usual care no-chamber group". Our rationale is that such a group could directly address the question of whether or not the sham low-pressure condition has clinical benefit.
115.	Page 21, line : I note your statement that "we disagree that it can be fully explained by potential physiological effects of sham". I have seen no argument advanced in this document to support this statement. I suggest adding the logic that has drawn you to this conclusion.	We concluded this based on the fact that the evidence of increased blood flow of the low-pressure conditions is not directly from samples with TBI and/or PTSD. We describe this in the paragraph preceding the "Limitations" section of the "Summary and Discussion": Proponents of HBOT for mild TBI and/or PTSD suggest that the main confusion in interpreting the findings of controlled HBOT trials is that the control groups of 1.2 to 1.3 ATA control groups have been mischaracterized as "sham". Although the Hyperbaric Oxygen Committee of the Undersea and Hyperbaric Medical Society defines HBOT treatment pressure as at least 1.4 times higher than sea level,[21,27] proponents of the 'mischaracterized sham' argument have suggested that lower pressures are actually active treatments with

		documented physiological and clinical effects. The evidence of increased blood flow effects of the low-pressure room air conditions that support the sham-control-mischaracterization argument are from samples with chronic toxic encephalopathy, autism, cerebrovascular injury, epilepsy, or migraine and not specific to TBI and also have the potential to the result of participation effects.[28]
116.	Appendix A I do not think this table is accurate – for example necrotizing fasciitis is approved by the UHMS, as is cyanide poisoning and ORN. I do not believe there are any FDA- approved indications that are not also UHMS indications. The full UHMS list from their website (I have exploded the list so you can see the indications more fully.): 1. Air or Gas Embolism • 2. Carbon Monoxide Poisoning (1. COP; 2. COP complicated by cyanide poisoning) • 3. Clostridial Myositis and Myonecrosis (Gas Gangrene) • 4. Crush Injury, Compartment Syndrome and Other Acute Traumatic Ischemias • 5. Decompression Sickness • 6. Arterial Insufficiencies (1. Central retinal artery occlusion; 2. Enhancement of healing in selected problem wounds) • 7. Severe Anemia • 8. Intracranial Abscess • 9. Necrotizing Soft Tissue Infections (Includes actinomyocis) • 10. Osteomyelitis (Refractory) • 11. Delayed Radiation Injury (Soft Tissue and Bony Necrosis) • 12. Compromised Grafts and Flaps • 13. Acute Thermal Burn Injury • 14. Idiopathic Sudden Sensorineural Hearing Loss (New! approved on October 8, 2011 by the UHMS Board of Directors)	We have corrected this Appendix to only include the 13 FDA-cleared indications – none of which are TBI or PTSD. We removed information about UHMS and CMS as none was specific to TBI or PTSD.
117.	The purpose stated in the SOW is correct, the draft should be corrected.	Corrected.

118.	Similarly, mention of the CCI pilot should be removed from the draft as it is not relevant to conducting "an evidence brief on the use of hyperbaric oxygen therapy (HBOT) for the treatment of traumatic brain injury (TBI), post-traumatic stress disorder (PTSD), or their co-occurrence." the use of this evidence brief would not necessarily be limited to the work CCI is doing.	Removed
119.	The following passages where CCI is mentioned should be removed: page 3 lines 26-30 page 7 lines 25-30 page 20 lines 16-25 page 20 line 53-page 21 line 4 page 21 lines 7-10 page 21 lines 42-46	Removed

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