

Hyperbaric Oxygen Therapy For Traumatic Brain Injury:

**A systematic review using the Rapid Evidence
Assessment of the Literature (REAL©) approach**

Samueli Institute

August 8, 2014

SAMUELI INSTITUTE'S MISSION



***To create a flourishing society through
the scientific exploration of wellness
and whole person healing.***

HEALTH AND WELLBEING

THROUGH



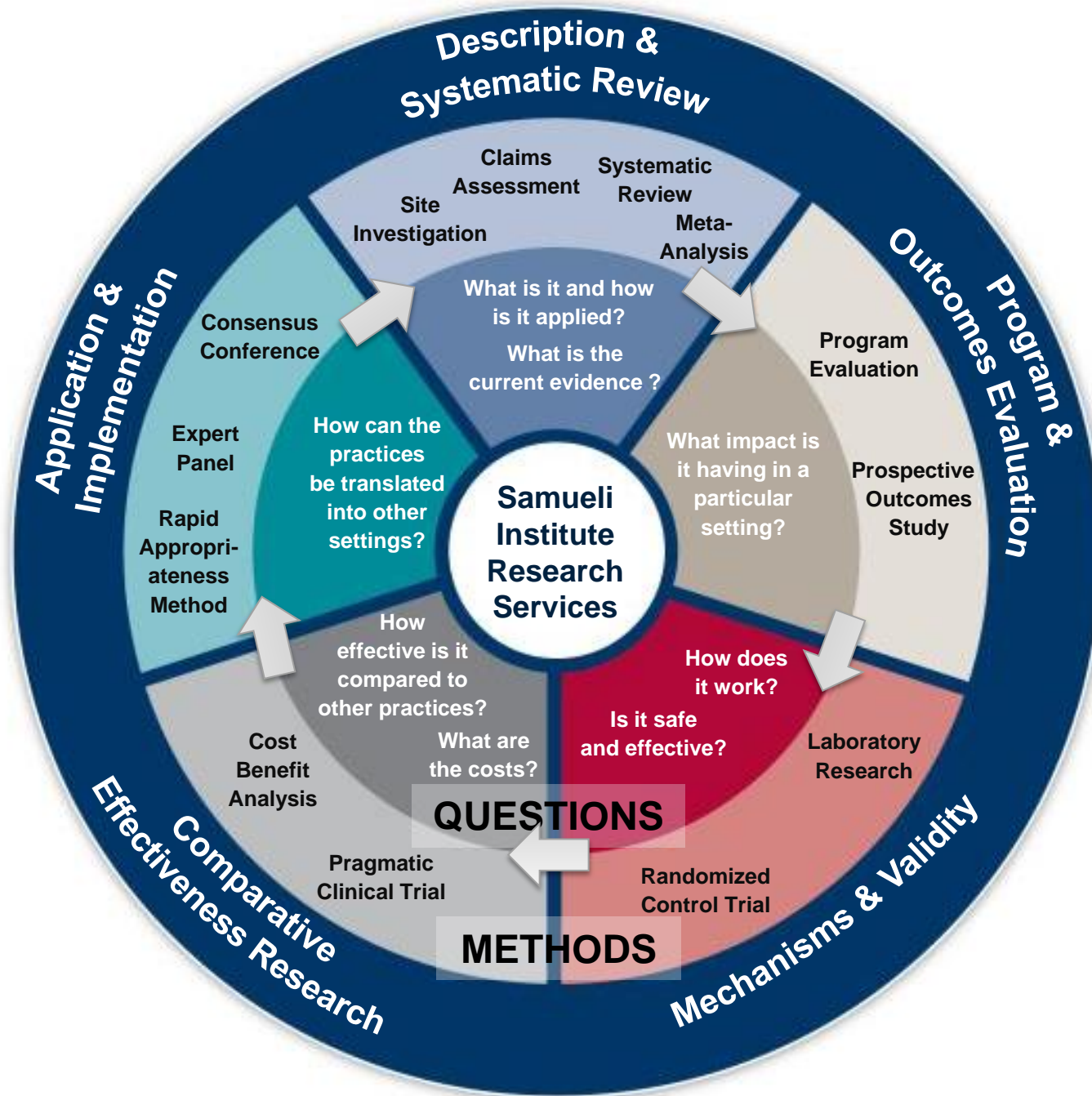
RESEARCH



INNOVATION



EDUCATION



Background

- Oxygen therapy becoming one of the most controversial forms of integrative medicine to enter the medical spotlight
- TBI is a leading cause of morbidity and mortality
- With increase in PTSD and TBI, case and anecdotal reports show positive effects but unclear what is producing effects
- There are concerns about toxicity from the oxygen and safety
- Little evidence has been brought into the public's eye to confirm or deny the validity of the current reports available
- SR methods are the “gold standard” evidence approach to sort out and assess validity of effects for benefit/risk in an objective, rigorous and transparent fashion

Agenda

- Introductions
- Objectives of the initiative
- Come to consensus on research question & PICO
- Discuss search strategy
- Detail the methodological process and steps to accomplish this project
- Review roles/responsibilities and timeline
- Next steps

Introductions to Steering Committee

Allene Creacy; Owner of Hyperbaric Healing Centers; Founder and President, American Association for Hyperbaric Awareness (AAHA)

Richard Ellenbogen; Professor and Chairman, Department of Neurological Surgery, University of Washington School of Medicine; Residency and Fellowship Director, UW Medicine Department of Neurological Surgery; Chief, Neurological Surgery, Harborview Medical Center

Kathy Helmick; Deputy Director, Traumatic Brain Injury, Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury

Irving Kirsch; Associate Director of the Program in Placebo Studies; Lecturer in Medicine at Harvard Medical School and Beth Israel Deaconess Medical Center; Professor Emeritus of Psychology at University of Hull, United Kingdom, and University of Connecticut

Richard Moon; Chairman, HBO2 Clinical Committee for Undersea and Hyperbaric Society; Duke University School of Medicine; Division Chief, General, Vascular, and Transplant Anesthesia; Medical Director, Hyperbaric Center; Professor of Anesthesiology

Regina McGlinchey; Co-Director of the Geriatric Neuropsychology Laboratory; Associate Professor of Psychology in the Department of Psychiatry at Harvard Medical School; Director of the Translational Research Center for TBI and Stress Disorders

Douglas H Smith; Director, Penn Center for Brain Injury and Repair; Robert A. Groff Professor of Neurosurgery; Vice-Chairman for Research & Education, Department of Neurosurgery, University of Pennsylvania

Gen Eric Schoomaker; MD, PhD, LTG (Ret) US Army; 42nd Surgeon General of the US Army; Former Commanding General of the US Army Medical Command; Scholar-in-Residence and Distinguished Professor of Military and Emergency Medicine at the Uniformed Services University of the Health Sciences, Bethesda, MD

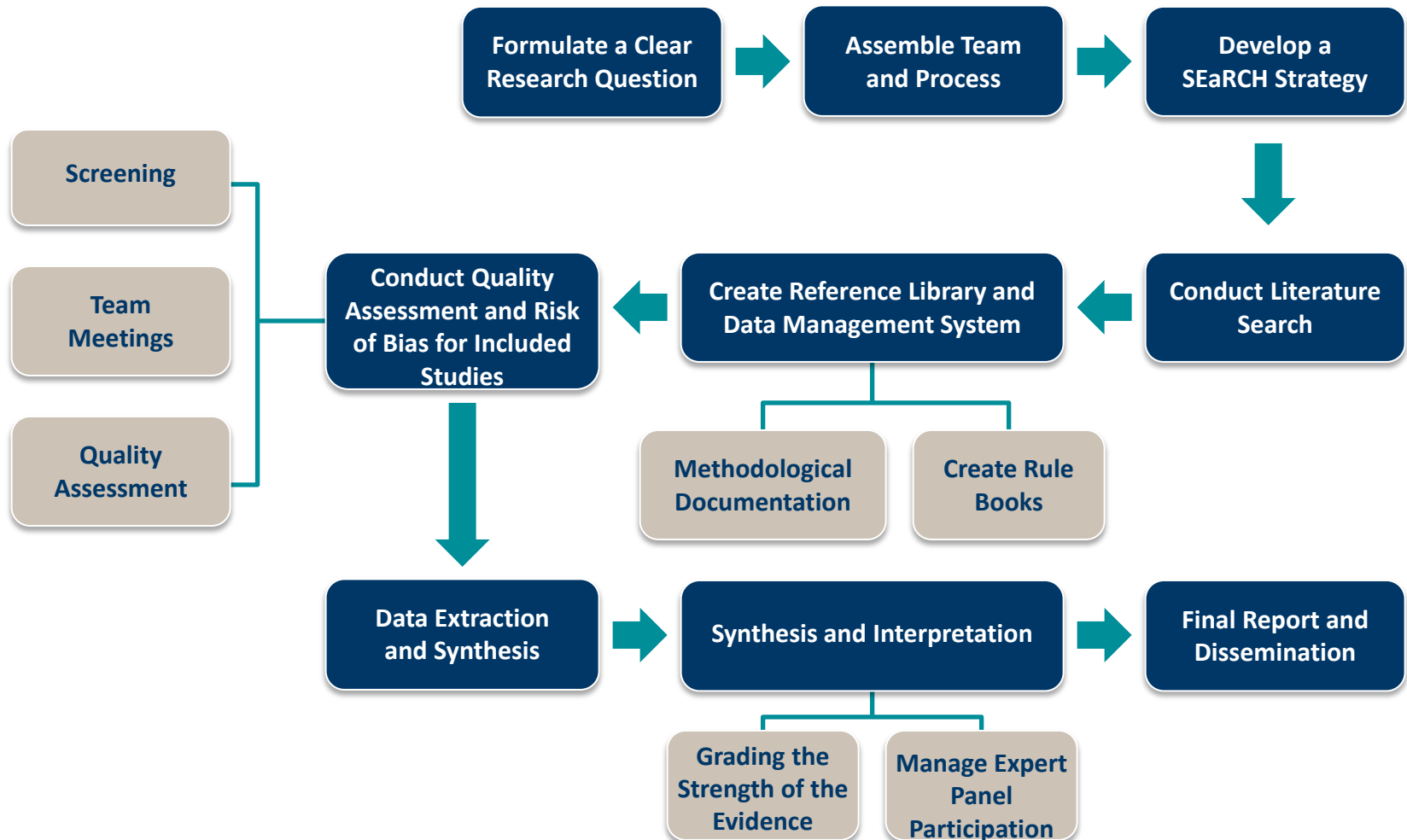
Objectives of current initiative under HBO

- To conduct a rigorous, transparent, high quality systematic review using Samueli Institute's Rapid Evidence Assessment of the Literature (REAL©) process to determine the current state of the science on the efficacy of Hyperbaric Oxygen (HBO₂) Therapy for patients suffering from the consequences of Traumatic Brain Injury (TBI)
- To develop initial recommendations based on the current state of the evidence for its clinical use, implementation, as well as next steps for future research.

Samueli Institute's Rapid Evidence Assessment of the Literature (REAL) Process

- Rapid assessment process using systematic review methodology
- Main Goals:
 - Survey the literature on a specific research question
 - Evaluate the quantity/quality of the literature
 - Assess the treatment's strength of evidence and risk/benefit
 - Identify gap areas, differences between studies reported and explore placebo factors
 - Suggest next steps for the field
- Streamlined, **rigorous** method that forms the foundation for determining appropriate **next steps** in policy, funding and research, and for making evidence-based clinical and field decisions on the use of the therapy, practice and program

Rapid Evidence Assessment of the Literature (REAL©) Systematic Review Process



Program Phase

Phase 1: Convene a Steering Committee (SC)

Phase 2: Conduct a REAL review of the literature

Phase 3: Convene a Roundtable to discuss REAL results and next steps toward translation

Phase 1: Convene a Steering Committee (SC)

- A diverse group of experts is essential to ensure the right research question(s) is being asked.
- *Responsibilities:*
 - Help to rigorously define the research question, scope and goal
 - Select 2-3 Subject Matter Experts (SMEs) to provide topical expertise and guidance to the review
 - Provide high level scientific oversight and guidance to assure program deliverables are valuable for the end-user.
 - Participate in the Roundtable

SME Members

- Subject Matter Experts (SMEs) are recruited to provide topical expertise and guidance, but are not intimately involved in the actual review process, performed independently by Samueli Institute
- *Responsibilities:*
 - Provide feedback and guidance to the review team at each phase of the review
 - Advise the review team regarding keywords/search strategy as necessary
 - Assess the overall quality of the literature as a whole (GRADE) once the review phase is complete with the guidance of the review manager, conducted independently
 - Participate in roundtable and final write up of reports



REAL Question and PICOS

What is the state of the science and evidence for effectiveness of hyperbaric oxygen therapy on the consequences of traumatic brain injury?

- P** **Population:** patients suffering from the consequences of traumatic brain injury (TBI) in both military and civilian populations
- I** **Intervention:** hyperbaric oxygen therapy
- C** **Control/Comparison:** not restricted
- O** **Outcome(s):** TBD
- S** Peer-reviewed, RCT **S** Study Design presented in the English language

Definitions

Traumatic Brain Injury (TBI)

- A structural injury and/or physiological disruption in brain function as a result of an external force resulting in the onset or worsening of clinical signs immediately post-event.

Management of Concussion/mTBI Working Group. VA/DoD Clinical Practice Guideline for Management of Concussion/Mild Traumatic Brain Injury. J Rehabil Res Dev. 2009;46(6):CP1–68. [\[PMID:20108447\]](#)

- We propose looking across the spectrum of TBI sequelae from acute to chronic effects and from mild to severe TBI, both in the military as well as civilian populations.

Hyperbaric Oxygen Therapy

- The inhalation of 100% oxygen inside a hyperbaric chamber that is pressurized to at least 1.4 times the atmospheric pressure at sea level (*gesell 2008 UHMS*)

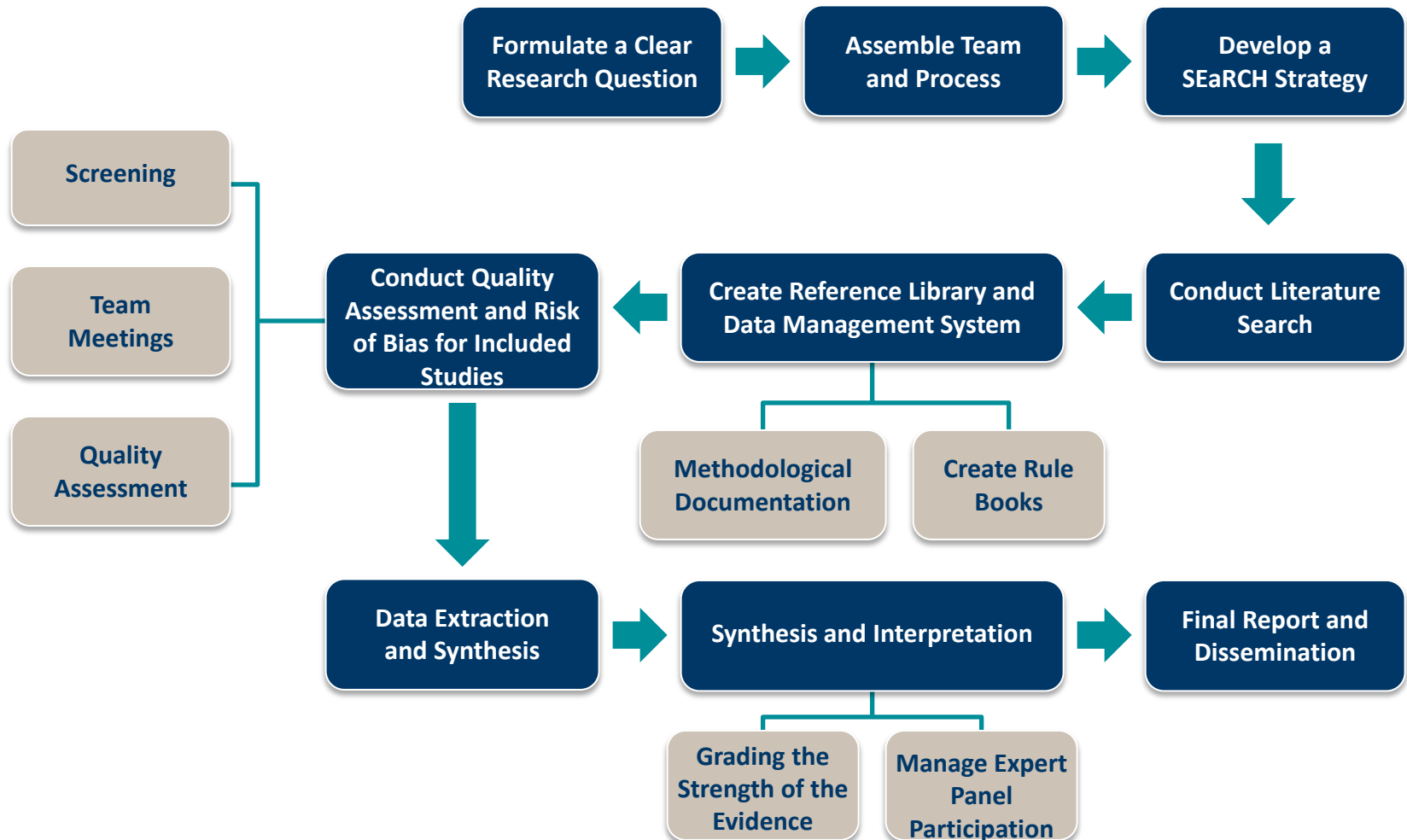
Refine PICO and Definitions

- Are these the right definitions for the population and intervention of interest?
- Are we interested in all TBI populations and just adults?
- What control/comparators are we interested in capturing?
- What do we consider a sham treatment?
- Are there specific dosage and regimen that we need to consider or just observe?
- What outcomes are of importance to this research question to capture through review? Function, Mortality, Disability..
- How do we ensure impact and meaning?

Research Question

What is the state of the science and evidence for **hyperbaric oxygen therapy** in the recovery from **traumatic brain injury**?

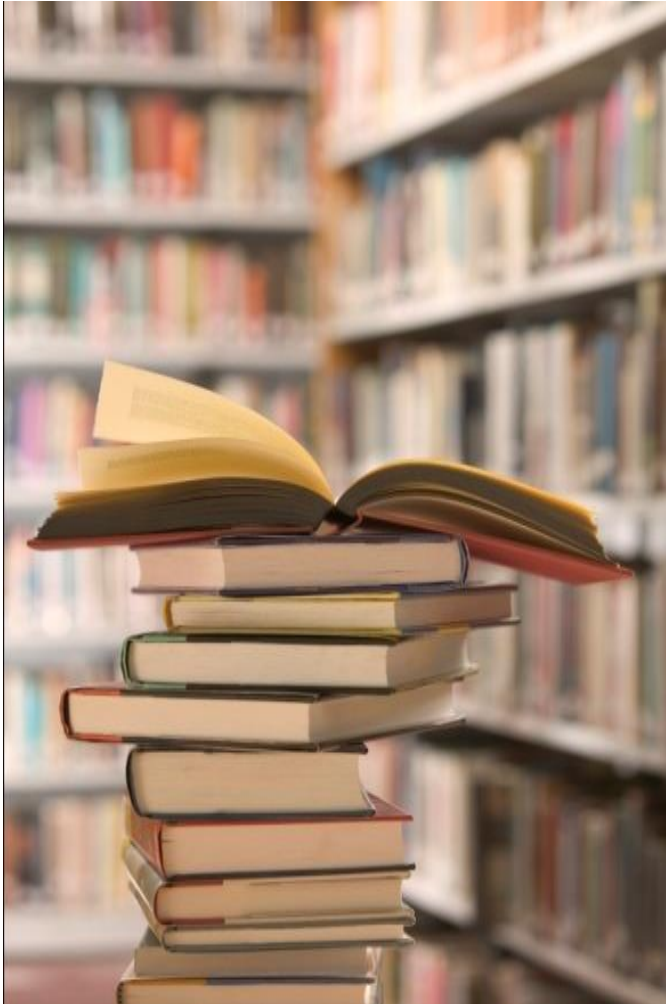
Rapid Evidence Assessment of the Literature (REAL©) Systematic Review Process



Introduction to SI Review team

- **Program Manager:** Cindy Crawford
- **Review Manager:** Lynn Teo
- **Team of Reviewers:** up to three trained reviewers identified from within the SI SRC
- **Research Coordinator:** Viviane Enslein

Phase 2: Conduct REAL once Research Question and PICO clearly defined



- Develop Search Strategy
- Conduct Search
- Screening Phase
- Review Phase
 - Quality Assessment of **individual** studies: SIGN 50
 - Data Extraction
- GRADE Analysis
 - Quality Assessment of **overall** literature pool: GRADE
 - Recommendations

Populations Search Terms

**MeSH Terms in red*

Brain injuries
Head Injuries
Craniocerebral Trauma

Intervention Search Terms

**MeSH Terms in red*

Hyperbaric oxygenation

“Hyperbaric oxygen therapy”

“Hyperbaric oxygen*”

“Hyperbaric therap*”

HBO

HBOT

CONDUCT SEARCH

PubMed/MEDLINE, Cochrane, EMBASE, CINAHL, PsycInfo, DORCTHIM, the Database of Randomised Trials in Hyperbaric Medicine, Undersea & Hyperbaric Medical Society, communicating with SC and SMEs

(Brain injuries or Head Injuries or Craniocerebral Trauma) AND
(Hyperbaric oxygenation or “Hyperbaric oxygen therapy” or “Hyperbaric oxygen*” or “Hyperbaric therap*” or HBO or HBOT)

Number of Pubmed Hits: 415

Limits: English language, not restricted to study design for initial screen to survey the literature but evaluating only the RCT for quality

Screening Phase

- **P:** Is the population comprised of subjects who have suffered traumatic brain injury?
- **I:** Does the intervention involve hyperbaric oxygen therapy?
- **C:** unrestricted
- **O:** TBD
- **S:** In this study an RCT presented in the English language?

Post Screening Kickoff to Review Phase Meeting

- Participants: SME's with the review team
- Responsibilities:
 - Review results of the screen phase
 - Discuss scope and impact for review phase
 - Review and approve rule books for review phase
 - Discuss Roles/responsibilities for remainder of review(s)
 - Next steps

Review Phase: Quality Assessment

SIGN 50 Criteria: Assessing Risk of Bias

1.1	The study addresses an appropriate and clearly focused question.
1.2	The assignment of subjects to treatment groups is randomized.
1.3	An adequate concealment method is used.
1.4	Subjects and investigators are kept 'blind' about treatment allocation
1.5	The treatment and control groups are similar at the start of the trial.
1.6	The only difference between groups is the treatment under investigation.
1.7	All relevant outcomes are measured in a standard, valid and reliable way.
1.8	What percentage of subjects in each treatment arm dropped out before the study was completed?
1.9	All subjects are analyzed in the groups to which they were randomly allocated (intention to treat analysis).
1.10	Where the study is carried out at more than one site, results are comparable for all sites.

Review Phase: *Data Extraction of Study Characteristics*

- P** • Population description
- Condition being studied
- **Informed consent**
- Sample entered/completed
- Compliance
- Intervention description / dosage
- I** • Treatment setting
- **Mono or multi-chamber social learning component**
- **Conditioning**
- Characteristics of researcher/practitioner
- C** • Control description/dosage
- Is there a placebo effect across the different studies

- O** • List of outcomes & time points of assessments
- Is outcome primary or secondary?
- Results based on outcome
- Effect size reported
- Can the data be used for meta-analysis pooling?
- Power calculations

Other

- Expectations
- Adverse events
- Cost analysis
- Author's main conclusions
- Funding source
- Protocol registered or published
- Disclosure/COI from authors
- Reviewers Comments

GRADE Process

Review Manager and SMEs convene to:

1. Share review result tables detailing individual studies
2. Train the SMEs in GRADE Methodology
3. SMEs independently GRADE the overall literature pool for each intervention/condition or subgroups identified
 - Confidence in the estimate of the effect
 - Magnitude of the effect size
 - Safety grade
 - Recommendations
4. Produce report summarizing GRADE results
5. Roundtable discussion

Phase 3: Roundtable Discussion

- Discuss and come to consensus on the overall **recommendations** made from the GRADE analysis for each of the subgroups assessed in the REAL process
- Discuss next steps needed for translation to occur

Deliverables

- Report of the REAL conducted summarizing the current state of the evidence
- Publication of manuscript written as systematic review report according to PRISMA guidelines

Timeline

Task	Estimated Time Commitment	Proposed Date
Virtual orientation/solidify research question/search strategy	2 hours	August 8, 2014
Post-screen meeting	2 hours	September 2014
GRADE Exercise	Up to 10 hours	November 2014
As an entire group, come to consensus regarding GRADE results, develop recommendations/next steps	Full day meeting at Samuelli (Alexandria, VA)	November-December 2014
Contribute to manuscript(s) writing	(optional)	December-March 2015

Thank you for joining us to make an important contribution!

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