



## Topic Brief: Traumatic Brain Injury

**Date:** 1/12/2021

**Nomination Number:** 799

**Purpose:** This document summarizes our assessment addressing a nomination submitted on 6/22/2018 through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

**Issue:** Traumatic brain injury (TBI) is a major cause of death and disability in the United States. Those who survive severe TBI, may face lasting disabilities, which impact not only their lives, but also the lives of their family and community. There are multiple methodologies for treating severe TBI and the Congress of Neurosurgeons seeks evidence to inform an update to their recommendations.

**Program Decision:** The EPC Program will not develop a new evidence review because we did not find enough primary studies addressing the concerns of this nomination.

**Key Findings:** We found 52 systematic reviews and 48 primary studies that addressed portions of the nomination. Few studies focused on similar comparisons across the 17 questions included in this nomination.

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### Background

Traumatic brain injury (TBI) is a major cause of death and disability in the United States. Those who survive severe TBI, may face lasting disabilities, which impact not only their lives, but also the lives of their family and community. There are multiple methodologies for treating severe TBI and the Congress of Neurosurgeons seeks evidence to inform an update to their recommendations.

This brief examines the literature for several aspects TBI care, including Decompressive Craniectomy (DC), osmotic treatment, seizure prophylaxis, cerebrospinal fluid (CSF) drainage, hypothermia, hyperventilation therapy, and drugs including barbiturates, sedatives, and steroids, as well as prophylaxis strategies to prevent ventilator-associated PICOTS.

The nominator plans to use the proposed systematic review to update a 2016 clinical practice guideline “Guidelines for the Management of Severe Traumatic Brain Injury.”

The key questions and PICOTS for this nomination are as follows.

KQ1: What are the effectiveness and harms of Decompressive Craniectomy (DC) for TBI treatment?

KQ2: What is the effectiveness of DC for TBI treatment on lowering ICP?

Systematic Reviews:

KQ3. What are the effectiveness and harms of hypertonic saline compared to mannitol for TBI treatment?

KQ4: What is the comparative effectiveness of phenytoin versus levetiracetam for the prevention of early and late seizures following TBI?

**Table 1. PICOTS for KQs 1-4**

<b>Key Questions</b>	KQ1 Effectiveness, clinical outcome	KQ2 Effectiveness, intermediate outcomes	KQ3 Hyperosmolar Therapy	KQ4 Seizure prophylaxis
<b>Population</b>	Adults with severe TBI	Adults with severe TBI	Adults with severe TBI	Adults with severe TBI
<b>Interventions</b>	DC	DC	Hypertonic saline	Levetiracetam for Seizure prophylaxis
<b>Comparators</b>	No DC	No DC	Mannitol	Phenytoin for seizure prophylaxis
<b>Outcomes</b>	Mortality, morbidity, Discharge status (home or institution), neurological function, harms of DC	Lowering Intracranial Pressure Monitoring (ICP)	Mortality, neurological function, Harms of intervention	Incidence seizures, timing (early, late). Neuropsychological function
<b>Timing</b>	All	All	All	All
<b>Setting</b>	Inpatient	Inpatient	Inpatient	Inpatient

**Abbreviations:** KQ: Key Question; TBI: Traumatic Brain Injury; Decompressive Craniectomy (DC)

**Cerebrospinal fluid (CSF) drainage**

5. Does CSF drainage impact mortality for adults with severe TBI?

6. What are the effectiveness and harms of continuous CSF drainage compared to intermittent CSF drainage?

**Table 1: PICOTS for KQs 5 and 6 on CSF Drainage**

	<b>KQ5</b>	<b>KQ6</b>
<b>Population</b>	Adults with severe TBI	Adults with severe TBI
<b>Intervention</b>	CSF drainage	Continuous CSF drainage
<b>Comparator</b>	No CSF drainage	Intermittent CSF drainage
<b>Outcomes</b>	Mortality	Intracranial pressure, harms
<b>Timing</b>	All	All
<b>Setting</b>	Inpatient	Inpatient

**Infection Prophylaxis**

This topic was divided into ventilator-associated infection and with external ventricular drain (EVD) infection topics.

7. What are the effectiveness and harms of strategies to prevent ventilator associated pneumonia in people with TBI?

8. What are the effectiveness and harms of strategies to prevent infections associated with external ventricular drains in people with TBI?

**Table 2: PICOTS for KQs 7 and 8 on Infection Prophylaxis**

	<b>KQ 7-Ventilator associated pneumonia</b>	<b>KQ 8-External ventricular drain (EVD) infection</b>
<b>Population</b>	Adults with severe TBI	Adults with severe TBI and an EVD
<b>Intervention</b>	Strategies to prevent Ventilator associated pneumonia	Strategies to prevent infections associated with EVD
<b>Comparator</b>	Other strategies to prevent Ventilator associated pneumonia Usual care	Other strategies to prevent infections associated with EVD Usual Care
<b>Outcomes</b>	Incidence of Ventilator associated pneumonia Harms	Incidence of infections associated with EVD Harms
<b>Timing</b>	All	All
<b>Setting</b>	Inpatient	Inpatient

### Deep Vein Thrombosis Prophylaxis

9. What are the effectiveness, comparative effectiveness and comparative harms of different pharmacologic Deep Vein Thrombosis (DVT) Prophylaxis agents in patients with TBI?

9a. How do harms vary by the timing of initiation of agent (e.g., bleeding risk)?

10. What are the comparative effectiveness of pharmacologic agents versus mechanical modalities for **DVT Prophylaxis** in patients with TBI?

11. What are the effectiveness of a protocol for DVT prophylaxis compared to no protocol?

**Table 3: PICOTS for KQs 9-11 on DVT Prophylaxis**

	<b>KQ8 and KQ8a - DVT pharmacologic prophylaxis</b>	<b>KQ10 - DVT pharmacologic vs. mechanical prophylaxis</b>	<b>KQ11 - DVT prophylaxis protocol</b>
<b>Population</b>	Adults with severe TBI	Adults with severe TBI	Adults with severe TBI
<b>Interventions</b>	Pharmacologic DVT prophylaxis (e.g. antiplatelet/ anticoagulants agents).	Pharmacologic DVT prophylaxis	DVT prophylaxis protocol
<b>Comparators</b>	Pharmacologic DVT prophylaxis No DVT prophylaxis	Mechanical DVT prophylaxis	No DVT prophylaxis protocol
<b>Outcomes</b>	Incidence of DVT Harms	Incidence of DVT	Incidence of DVT
<b>Timing</b>	All	All	All
<b>Setting</b>	Inpatient	Inpatient	Inpatient

### Prophylactic Hypothermia

12. What are the effectiveness and harms of prophylactic hypothermia for TBI treatment?

a. Do outcomes differ by length of treatment?

13. What are the effectiveness and harms of head-only cooling compared to systemic hypothermia?

**Table 4: PICOTS for KQ 12 and 13 on Prophylactic Hypothermia**

	<b>KQ12 and KQ12a - Prophylactic Hypothermia - Effectiveness, clinical outcomes</b>	<b>KQ13 - Prophylactic Hypothermia - Head-only vs. systematic hypothermia</b>
<b>Population</b>	Adults with severe TBI	Adults with severe TBI
<b>Intervention</b>	Prophylactic hypothermia	Head-only
<b>Comparator</b>	No hypothermia	Systemic
<b>Outcomes</b>	Mortality, neurological function, Harms of intervention	Mortality, neurological function, harms
<b>Timing</b>	All	All
<b>Setting</b>	Inpatient	Inpatient

## Ventilation Therapy

14. What are the effectiveness and harms of hyperventilation?

a. Do outcomes vary by treatment duration?

**Table 5: PICOTS on KQ 14 on Ventilation therapy**

	<b>KQ14, 14a – Ventilation Therapy</b>
<b>Population</b>	Adults with severe TBI
<b>Intervention</b>	Hyperventilation, Prolonged duration of treatment (It was 5 days in Muizelaar 1991 article cited.)
<b>Comparator</b>	Usual care
<b>Outcomes</b>	Mortality, neurological function
<b>Timing</b>	All
<b>Setting</b>	Inpatient

## Drugs (Anesthetics, analgesics, sedatives, steroids)

15a. What are the effectiveness and harms of using barbiturates prophylactically in TBI patients?

15b. What are the effectiveness and harms of using barbiturates for TBI treatment?

16. What are the effectiveness and harms of sedatives for TBI treatment?

17. What are the effectiveness and harms of steroids for TBI treatment?

**Table 6: PICOTS on KQ 15-17 on Drugs**

	<b>KQ15a and 15b - Barbiturates</b>	<b>KQ16 -Sedatives</b>	<b>KQ17 - Steroids</b>
<b>Population</b>	Adults with severe TBI	Adults with severe TBI	Adults with severe TBI
<b>Intervention</b>	Prophylactic barbiturates	Sedatives	Steroids
<b>Comparator</b>	No prophylactic barbiturates	No sedatives	No steroids
<b>Outcomes</b>	Mortality, intracranial hypertension	Mortality, neurologic function	Mortality, neurologic function
<b>Timing</b>	All	All	All
<b>Setting</b>	Inpatient	Inpatient	Inpatient

**Table 7. Literature identified for each Question**

Key Question	Duplication	Feasibility
<p><b>KQs 1-4</b></p> <p>KQ1-2 – Decompressive Craniectomy</p>	<p>Total number of identified systematic reviews: 7 (Abraham et al., 2017a; Alotaibi et al., 2017; Barthelemy, Melis, Gordon, Ullman, &amp; Germano, 2016; Grindlinger, Skavdahl, Ecker, &amp; Sanborn, 2016; Phan et al., 2017; G. G. Tsaousi et al., 2018; D. Zhang et al., 2017)( Abraham et al., 2017a; Alotaibi et al., 2017; Barthelemy et al., 2016; Grindlinger et al., 2016; Phan et al., 2017; G. G. Tsaousi et al., 2018; D. Zhang et al., 2017))</p>	<p><u>Size/scope of review</u> Relevant Studies Identified:</p> <p>Compared to No DC: 4: (Honeybul, 2017; Hutchinson et al., 2016; Nirula et al., 2014; Vilcinis, Bunevicius, &amp; Tamasauskas, 2017))</p> <p>Not Compared to No DC: 9: (Badke et al., 2018; Chaturvedi et al., 2016; Hartings et al., 2014; Honeybul &amp; Ho, 2016; Kapapa, Brand, Wirtz, &amp; Woischneck, 2016; A. D. Khan et al., 2017; B. Khan et al., 2016; Moskowitz et al., 2018; Songara, Gupta, Jain, Rege, &amp; Masand, 2016)( (Badke et al., 2018; Chaturvedi et al., 2016; Hartings et al., 2014; Honeybul &amp; Ho, 2016; Kapapa et al., 2016; A. D. Khan et al., 2017; B. Khan et al., 2016; Moskowitz et al., 2018; Songara et al., 2016))</p> <p>Clinicaltrials.gov: 1: (Lilja-Cyron, 2015({Lilja-Cyron, 2015 #802({Lilja-Cyron, 2015 #802}))</p>
<p>KQ3 – Hyperosmolar Therapy</p>	<p>Total number of identified systematic reviews: 8: (Alnemari, Krafcik, Mansour, &amp; Gaudin, 2017; Berger-Pelleiter, Emond, Lauzier, Shields, &amp; Turgeon, 2016; Berger-Pelletier, Emond, Lauzier, Shields, &amp; Turgeon, 2016; Burgess, Abu-Laban, Slavik, Vu, &amp; Zed, 2016; J. Gu, Huang, Huang, Sun, &amp; Xu, 2019; Pasarikovski, Alotaibi, Al-Mufti, &amp; Macdonald, 2017; Tsaousi, Stazi, Cinicola, &amp; Bilotta, 2018; W. Zhang et al., 2019)( Alnemari et al., 2017; Berger-Pelleiter et al., 2016; Berger-Pelletier et al., 2016; Burgess et al., 2016; J. Gu et al., 2019; Pasarikovski et al., 2017; G. Tsaousi et al., 2018; W. Zhang et al., 2019))</p>	<p><u>Size/scope of review</u> Relevant Studies Identified: 2: (Jagannatha, Sriganesh, Devi, &amp; Rao, 2016; H. Wang, Cao, Zhang, Ge, &amp; Bie, 2017)( (Jagannatha et al., 2016; H. Wang et al., 2017))</p> <p><u>Clinicaltrials.gov: 0</u></p>
<p>KQ4 – Seizure Prophylaxis</p>	<p>Total number of identified systematic reviews: 10: (Bakr &amp; Belli, 2018; Calnan, D'Agostino, Reynolds, &amp; Bekelis, 2017; Chaari, Mohamed, Abdelhakim, Kauts, &amp; Casey, 2017; N. R. Khan et al., 2016; Piccenna, Shears, &amp; O'Brien, 2017; Wat et al., 2019; Won et al., 2017; Xu et al., 2016; Yang, Zheng, Xu, &amp; Wang, 2016; Zhao et al., 2018)( (Bakr &amp; Belli, 2018; Calnan et al., 2017; Chaari et al., 2017; N. R. Khan et al., 2016; Piccenna et al., 2017; Wat et al., 2019; Won et al., 2017; Xu et al., 2016; Yang et al., 2016; Zhao et al., 2018))</p>	<p><u>Size/scope of review</u> Relevant Studies Identified: 1: (S. A. Khan et al., 2016)( (S. A. Khan et al., 2016))</p> <p><u>Clinicaltrials.gov: 0</u></p>

Key Question	Duplication	Feasibility
<b>KQs 5-9</b>		
KQ5 – CSF Drainage	Total number of identified systematic reviews: 0	<u>Size/scope of review</u> Relevant Studies Identified: None  <u>Clinicaltrials.gov: 0</u>
KQ6 – CSF Continuous Drainage	Total number of identified systematic reviews: 0	<u>Size/scope of review</u> Relevant Studies Identified:  Non-RCT: 0  <u>Clinicaltrials.gov: 0</u> (Valadka, 2015)(Valadka, 2015)(Valadka, 2015)(Valadka, 2015)(Valadka, 2015)(Valadka, 2015)(Valadka, 2015)
KQ7 - Ventilator associated pneumonia	Total number of identified systematic reviews: 1 ((Zhu, Chen, Pan, Qiu, & Xu, 2018)) (Zhu et al., 2018)	<u>Size/scope of review</u> Relevant Studies Identified: 0  <u>Clinicaltrials.gov: 1: ((Abdelaziz, 2017))</u>
KQ8 - External ventricular drain (EVD) infection	Total number of identified systematic reviews: 1: ((Zhu et al., 2018))	<u>Size/scope of review</u> Relevant Studies Identified:  Non-RCT: 1 (Working Group on Neurosurgical Outcomes et al., 2016)  <u>Clinicaltrials.gov: 0</u>
<b>KQs 9-17</b>		
KQ9 and KQ9a - DVT pharmacologic prophylaxis	Total number of identified systematic reviews: 6 ((Abdel-Aziz, Dunham, Malik, & Hileman, 2015; Hachem, Mansouri, Scales, Geerts, & Pirouzmand, 2018; V. M. Lu, Alvi, Rovin, & Kasper, 2018; Maegele et al., 2017; Margolick et al., 2018; Mesa Galan, Egea-Guerrero, Quintana Diaz, & Vilches-Arenas, 2016))	<u>Size/scope of review</u> Relevant Studies Identified:  RCTs: 4 (Albrecht et al., 2014; Daley, Ali, & Brown, 2015; Frisoli et al., 2017; Skrifvars et al., 2017)  Non-RCTs: 9 (Benjamin, Recinos, Aiolfi, Inaba, & Demetriades, 2017; Byrne et al., 2016; Matsushima et al., 2016; Meyer et al., 2017; Nyquist et al., 2016; Pastorek et al., 2014; Sumislawski, Kornblith, Conroy, Callcut, & Cohen, 2018; Tracy, Dunne, O'Neal, & Clayton, 2016; Van Gent et al., 2014)  <u>Clinicaltrials.gov: 1 ((Pirouzmand, 2018))</u>
KQ10 - DVT pharmacologic vs. mechanical prophylaxis	Total number of identified systematic reviews: 0	<u>Size/scope of review</u> Relevant Studies Identified: 0  <u>Clinicaltrials.gov: 0</u>
KQ11 - DVT prophylaxis protocol	Total number of identified systematic reviews: 0	<u>Size/scope of review</u> Relevant Studies Identified: 0  <u>Clinicaltrials.gov: 0</u>

<b>Key Question</b>	<b>Duplication</b>	<b>Feasibility</b>
KQ12 and KQ12a – Hypothermia Effectiveness, clinical outcomes	Total number of identified systematic reviews: 7  (Crompton et al., 2017; Dunkley & McLeod, 2017; Fischer et al., 2017; Leng, 2017; Lewis, Evans, Butler, Schofield-Robinson, & Alderson, 2017; Madden et al., 2017; Watson, Shepherd, Rhodes, & Andrews, 2018)  Protocol: 1 (Perdomo, 2018) (Note: Published on 1/2/2020: William A. Flórez et al., "Hypothermia for refractory intracranial hypertension after severe head trauma," Argentine Journal of Neurosurgery , see January 2, 2020, <a href="http://aanc.org.ar/ranc/items/show/1232">http://aanc.org.ar/ranc/items/show / 1232 .</a> )	<u>Size/scope of review</u> Relevant Studies Identified:  14 RCT: (P. J. Andrews et al., 2018; P. J. Andrews et al., 2015; P. J. D. Andrews et al., 2017; Cooper et al., 2018; Feng et al., 2017; Flynn, Rhodes, & Andrews, 2015; Hifumi et al., 2017; Idris, Zenian, Muzaimi, & Hamid, 2014; Kaneko et al., 2018; Lei et al., 2015; Maekawa et al., 2015; Nichol et al., 2015; Suehiro et al., 2015; Tang et al., 2017)  4 non-RCT: (Miyata et al., 2016; Oshorov et al., 2014; Park, Kogeichi, Shida, & Nakase, 2018; Rim et al., 2016)  <u>Clinicaltrials.gov</u> : 2: ((G. Gao, 2018; Schmitt, 2014))(G. Gao, 2018; Schmitt, 2014)
KQ13 - Head-only vs. systemic hypothermia	Total number of identified systematic reviews: 0	<u>Size/scope of review</u> Relevant Studies Identified: 0  <u>Clinicaltrials.gov</u> : 0
KQ14, 14a – Ventilation Therapy	Total number of identified systematic reviews: 0	<u>Size/scope of review</u> Relevant Studies Identified:  Non-RCTs: 1 (Chesnut et al., 2018)  <u>Clinicaltrials.gov</u> : 0
KQ15a and 15b - Barbiturates	Total number of identified systematic reviews: 2 (Abraham et al., 2017b; Alnemari et al., 2017))	<u>Size/scope of review</u> Relevant Studies Identified:  Non-RCTs: 3 (Alali et al., 2014; Colton et al., 2014; Nirula et al., 2014)  <u>Clinicaltrials.gov</u> : 0
KQ16 - Sedatives	Total number of identified systematic reviews: 3 (Alnemari et al., 2017; J. W. Gu et al., 2014; Gultekin et al., 2016))  Protocol: 1 (Burry et al., 2017)) (Full duplication)	<u>Size/scope of review</u> Relevant Studies Identified:  Non-RCTs: 8 (J. Gao et al., 2019; Humble et al., 2016; Khan, Kumar, Singh, Singh, & Mathur, 2017; Li, Zhang, Wu, & Hu, 2016; Pajoumand et al., 2016; Singh, Chouhan, Bindra, & Radhakrishna, 2018; Tang et al., 2017; Yan et al., 2018)  <u>Clinicaltrials.gov</u> : 1: ((Chen, 2019))(Chen, 2019)

Key Question	Duplication	Feasibility
KQ17 - Steroids	Total number of identified systematic reviews: 7  (Asehnoune, Vourc'h, & Roquilly, 2019; Beez, Steiger, & Etminan, 2017; X. Y. Lu, Sun, Li, & Lu, 2016; Ma, Huang, Qin, You, & Zeng, 2016; Martino et al., 2018; Pan, Zhao, Huang, Xiao, & Li, 2019; Z. Wang et al., 2016)	<u>Size/scope of review</u> Relevant Studies Identified:  RCTs: 2 (Asehnoune et al., 2014; Goldstein et al., 2017)  Non-RCTs: 1 (Oliynyk, Pereviznyk, Yemiashev, & Shlifirchyk, 2016)( Oliynyk et al., 2016))  <a href="https://clinicaltrials.gov">Clinicaltrials.gov</a> : 0

Abbreviations: KQ=key question; RCT=randomized controlled trial

## Assessment Methods

See Appendix A.

## Summary of Literature Findings

We found 52 systematic reviews and 48 primary studies that addressed portions of the nomination.

For KQ1-2 (Decompressive Craniectomy), we found previous systematic reviews, one of which appeared to be of higher quality, so there seems to be duplication. (D. Zhang et al., 2017)

For both KQ3 (Hyperosmolar Therapy) and KQ4 (Seizure Prophylaxis), there were several systematic reviews, which may partially cover the evidence needs. A review is not feasible for either topic, due to the small number of studies (2 for KQ3 and 1 for KQ4.)

For KQs 5 and 6 (CSF Drainage), we found no recent systematic reviews or studies.

For KQs 7 and 8 (infection prophylaxis for ventilator-associated pneumonia and EVD infections respectively), there is 1 general evidence review on infection prophylaxis. This review only partially answers the questions. There was 1 cohort study for EVD infection.

For KQs 9 and 9a (DVT pharmacologic prophylaxis), there are 6 systematic reviews that partially answer the questions. Only 1 of these 6 reviews attempted to address pharmacologic vs. mechanical DVT prophylaxis (KQ6), but the review was unable to compare the two. For KQs 9 and 9a, there were only 4 RCTs and 9 non-RCTs; KQ 10 did not have any trials that met criteria. There were no reviews or trials addressing KQ11 (DVT prophylaxis protocol).

For KQ12, 12a, and 13 (Hypothermia), there are 7 reviews, including a 2017 Cochrane review. This 2017 review is duplicative. There is a recently 2018 RCT and a 2018 non-RCT that were published after the review. In addition to these studies, there were 13 other older RCTs, and 3 other older non-RCTs. There are no reviews or studies on head-only hypothermia compared to systemic hypothermia (KQ13).

For KQ14 and 14a (Ventilation therapy), there are no reviews and only 1 non-RCT study.

For KQ15a and 15b (Barbiturates), there are 2 reviews that only partially addressed the questions. There were 3 non-RCTs that addressed barbiturates



For KQ16 (Sedatives), there are 3 reviews that only partially address the question; however, there is a protocol for a Cochrane review that fully addresses the question. This upcoming review will be duplicative. As for studies, there were only 8 non-RCTs.

For KQ17 (Steroids), there are 7 reviews that partially address the question. There are only 2 RCTs and 1 non-RCT addressing this topic.

See Appendix B for detailed assessments of all EPC selection criteria.

### **Summary of Selection Criteria Assessment**

The topic of this nomination pertains to important healthcare interventions for the management of severe TBI. We found systematic reviews that cover portions of the nomination; and too few studies to support a new systematic review.

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### **Author**

Kim Wittenberg

**Conflict of Interest:** The investigator does not have any affiliations or financial involvement that conflicts with the material presented in this report.

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## Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

### Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

### Desirability of New Review/Absence of Duplication.

We searched for high-quality, completed or in-process evidence reviews published in the last three years (dates shown below) on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
  - AHRQ Evidence Reports <https://www.ahrq.gov/research/findings/evidence-based-reports/index.html>
  - EHC Program <https://effectivehealthcare.ahrq.gov/>
  - US Preventive Services Task Force <https://www.uspreventiveservicestaskforce.org/>
  - AHRQ Technology Assessment Program <https://www.ahrq.gov/research/findings/ta/index.html>
- US Department of Veterans Affairs Products publications
  - Evidence Synthesis Program <https://www.hsrd.research.va.gov/publications/esp/>
  - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program <https://www.healthquality.va.gov/>
- Cochrane Systematic Reviews <https://www.cochranelibrary.com/>
- University of York Centre for Reviews and Dissemination database <https://www.crd.york.ac.uk/CRDWeb/>
- PROSPERO Database (international prospective register of systematic reviews and protocols) <http://www.crd.york.ac.uk/prospéro/>
- PubMed <https://www.ncbi.nlm.nih.gov/pubmed/>
- Campbell Collaboration <http://www.campbellcollaboration.org/>
- McMaster Health System Evidence <https://www.healthsystemevidence.org/>
- UBC Centre for Health Services and Policy Research <http://chspr.ubc.ca/>
- Joanna Briggs Institute <http://joannabriggs.org/>
- WHO Health Evidence Network <http://www.euro.who.int/en/data-and-evidence/evidence-informed-policy-making/health-evidence-network-hen>

### Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

## Feasibility of New Evidence Review

For each of the three parts, we conducted a limited literature search in PubMed for the last five years. (Dates of each search are listed below.) We classified identified studies by question and study design to estimate the size and scope of a potential evidence review.

### Search Strategy

KQs 1-4

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Search range: January 2014 to December 05, 2018

#	Searches Results	Type
1	Brain injuries, traumatic/ or brain concussion/ or post-concussion syndrome/ or brain contusion/ or chronic traumatic encephalopathy/ or brain hemorrhage, traumatic/ or brain stem hemorrhage, traumatic/ or cerebral hemorrhage, traumatic/ or diffuse axonal injury/ or cerebrovascular trauma/ or craniocerebral trauma/ or contrecoup injury/ or epilepsy, post-traumatic/ or coma, post-head injury/ or head injuries, closed/ or head injuries, penetrating/ or intracranial hemorrhage, traumatic/ or hematoma, epidural, cranial/ or hematoma, subdural/ or hematoma, subdural, acute/ or hematoma, subdural, chronic/ or hematoma, subdural, intracranial/ or subarachnoid hemorrhage, traumatic/	46935
2	(TBI or sTBI or bTBI or concuss* or contusion* or coup-contrecoup or "diffuse axonal" or ((blunt or injur* or penetrat* or trauma* or severe*) adj2 (brain or crania* or cranio* or cerebr* or cortex or head or skull)) or postconcuss* or post-concuss* or posttrauma* or post-trauma*).tw,kf.	177749
3	or/1-2	195867
4	(animals/ not humans/) or (rat or rats).tw.	4721496
5	3 not 4	167830
6	limit 5 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")	80509
7	5 not (Adolescent/ or Child/ or Infant/ or Pediatrics/ or (child or children or infant or infants or infancy or newborn or newborns or new-born or new-borns or neonate or neonates or neonatal or neo-nate or neo-nates or neo-natal or neonatology or premature or prematures or pre-mature or pre-matures or preterm or pre-term or postnatal or post-natal or baby or babies or suckling or sucklings or toddler or toddlers or childhood or schoolchild or schoolchildren or childcare or child-care or youngster or youngsters or preschool or pre-school or kid or kids or boy or boys or girl or girls or adolescent or adolescents or adolescence or pre-adolescent or pre-adolescents or pre-adolescence or schoolage or schoolboy or schoolboys or schoolgirl or schoolgirls or pre-puber or pre-pubers or pre-puberty or prepuber or prepubers or prepuberty or puber or pubers or puberty or puberal or teenager or teenagers or teens or youth or youths or underaged or under-aged or Pediatric or Pediatrics or Paediatric or Paediatrics or children* or schoolchild* or infant or infants or infancy or adolesc* or pediat* or paediat* or neonat* or toddler* or teen or teens or teenager* or preteen* or newborn* or postneonat* or postnatal* or puberty or preschool* or suckling* or juvenile or new born or new borns or new-born* or neo-nat* or neonat* or perinat* or underag* or under age or under aged or youth* or kinder* or pubescen* or prepubescen* or prepuberty or school age or schoolage or school ages or schoolage*).ti,ab,kf. or (NICU or PICU or young or one year old or two year old or three year old or four year old or five year old or six year old or seven year old or eight year old or nine year old or ten year old or eleven year old or twelve year old or thirteen year old or fourteen year old or fifteen year old or sixteen year old or seventeen year old or eighteen year old or 1 year old or 2 year old or 3 year old or 4 year old or 5 year old or 6 year old or 7 year old or 8 year old or 9 year old or 10 year old or 11 year old or 12 year old or 13 year old or 14 year old or 15 year old or 16 year old or 17 year old or 18 year old or two years old or three years old or four years old or five years old or six years old or seven years old or eight years old or nine years old or ten years old or eleven years old or twelve years old or thirteen years old or fourteen years old or fifteen years old or sixteen years old or seventeen years old or eighteen years old or 2 years old or 3 years old or 4 years old or 5 years old or 6 years old or 7 years old or 8 years old or 9 years old or 10 years old or 11 years old or 12 years old or 13 years old or 14 years old or 15 years old or 16 years old or 17 years old or 18 years old).ti.)	109697

#	Searches Results	Type
8	or/6-7	140195
9	Decompressive Craniectomy/ or Decompression, Surgical/ or Trephining/ or (craniectom* or craniot* or trephin* or (decompress* adj2 (hemicraniect* or hemi-craniectom* or hypertens* or intracran* or neurosurg* or surg*))).tw,kf.	39805
10	and/8-9	3482
11	limit 10 to english language	2868
12	limit 11 to (adaptive clinical trial or clinical trial, all or clinical trial or controlled clinical trial or pragmatic clinical trial or randomized controlled trial)	176
13	limit 12 to yr="2013 -Current"	76
14	limit 11 to (meta analysis or systematic reviews)	101
15	limit 14 to yr="2015 -Current"	47
16	Mannitol/ or Saline Solution, Hypertonic/ or (hyperosmol* or "osmolar concentration" or mannitol or (hyperton* adj3 saline)).tw,kf.	34582
17	and/8,16	738
18	limit 17 to english language	621
19	limit 18 to (adaptive clinical trial or clinical trial, all or clinical trial or controlled clinical trial or pragmatic clinical trial or randomized controlled trial)	84
20	limit 19 to yr="2013 -Current"	25
21	limit 18 to (meta analysis or systematic reviews)	58
22	limit 21 to yr="2015 -Current"	18
23	Phenytoin/ or (antiepileptic* or anti-epileptic* or levetiracetam or phenytoin).tw,kf.	41555
24	and/8,23	742
25	limit 24 to english language	647
26	limit 25 to (adaptive clinical trial or clinical trial, all or clinical trial or controlled clinical trial or pragmatic clinical trial or randomized controlled trial)	52
27	limit 26 to yr="2013 -Current"	15
28	limit 25 to (meta analysis or systematic reviews)	58
29	limit 28 to yr="2015 -Current"	27

KQs 5-11

Feasibility

MEDLINE(PubMed) searched on: April 4, 2019

Concept	Search String
<b>Cerebrospinal Fluid Drainage</b>	
Traumatic Brain Injury	((("Brain Injuries, Traumatic/therapy"[Mesh]) OR "traumatic brain Injury"[Title/Abstract]) OR TBI[Title/Abstract]) OR mTBI[Title/Abstract]
AND	
Cerebrospinal Fluid Drainage	(((((("Cerebrospinal Fluid"[Mesh] OR "cerebrospinal fluid" [Subheading])) OR "Cerebrospinal Fluid Pressure"[Mesh]) OR "cerebrospinal fluid"[Title/Abstract]) OR CSF[Title/Abstract])) AND ((drain[Title/Abstract] OR drainage[Title/Abstract] OR shunt[Title/Abstract]))
AND	
Limits: last 5 years & English	
Total N=75	
SR N=1 EndNote group CSF SR	Systematic[sb]

<b>Concept</b>	<b>Search String</b>
<b>RCT</b> N=13 EndNote Group CSF RCT	((((((((groups[tiab])) OR (trial[tiab])) OR (randomly[tiab])) OR (drug therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt]))
Other N=61 EndNote Group CSF Other	
<b>ClinicalTrials.gov</b>	Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation Studies   Traumatic Brain Injury   Cerebrospinal Fluid Drainage   Adult, Older Adult   Last update posted from 04/04/2014 to 04/04/2019
<b>Thrombosis Prophylaxis</b>	
Traumatic Brain Injury	((("Brain Injuries, Traumatic/therapy"[Mesh]) OR "traumatic brain Injury"[Title/Abstract]) OR TBI[Title/Abstract]) OR mTBI[Title/Abstract]
AND	
Thrombosis Prophylaxis	((("Thromboembolism/prevention and control"[Mesh]) OR "Thrombosis/prevention and control"[Mesh])) OR (((thromboembolism[Title/Abstract] OR thrombosis[Title/Abstract] OR thromboembolic[Title/Abstract])) AND ((prevention[Title/Abstract] OR control[Title/Abstract] OR prophylactic[Title/Abstract] OR prophylaxis[Title/Abstract])))
AND	
Limits: last 5 years & English	
Total N=47	
<b>SR</b> N=3 EndNote group Thrombosis SR	Systematic[sb]
<b>RCT</b> N=20 EndNote group Thrombosis RCT	((((((((groups[tiab])) OR (trial[tiab])) OR (randomly[tiab])) OR (drug therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt]))
Other N=24 EndNote group Thrombosis Other	
<b>ClinicalTrials.gov</b>	thrombosis OR thrombolytic   Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation Studies   Traumatic Brain Injury   Adult, Older Adult   Last update posted from 04/04/2014 to 04/04/2019
<b>Infection Prophylaxis</b>	
Traumatic Brain Injury	((("Brain Injuries, Traumatic/therapy"[Mesh]) OR "traumatic brain Injury"[Title/Abstract]) OR TBI[Title/Abstract]) OR mTBI[Title/Abstract]
AND	
Infection Prophylaxis	((("Infection/prevention and control"[Mesh])) OR "Infection Control"[Mesh]) OR ("Anti-Infective Agents"[Mesh] OR "Anti-Infective Agents" [Pharmacological Action] OR "Anti-Infective Agents, Local"[Mesh])) OR (((infection[Title/Abstract] OR infective[Title/Abstract] OR anti-infective[Title/Abstract] OR antibiotic[Title/Abstract])) AND ((prevention[Title/Abstract] OR control[Title/Abstract] OR prophylactic[Title/Abstract] OR prophylaxis[Title/Abstract])))
Limits: last 5 years & English	
Total N=300	
<b>SR</b> N=11 EndNote group Infection SR	Systematic[sb]
<b>RCT</b> N=158 EndNote group Infection RCT	((((((((groups[tiab])) OR (trial[tiab])) OR (randomly[tiab])) OR (drug therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt]))
Other N=131 EndNote group Infection Other	

Concept	Search String
ClinicalTrials.gov	Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation Studies   Traumatic Brain Injury   Anti-Infective Agents   Adult, Older Adult   Last update posted from 04/04/2014 to 04/04/2019

KQs 12-17

Ovid MEDLINE(R) ALL 1946 to September 13, 2019

Date searched: September 16, 2019

#	Searches	Results
1	Brain injuries, traumatic/ or brain concussion/ or post-concussion syndrome/ or brain contusion/ or chronic traumatic encephalopathy/ or brain hemorrhage, traumatic/ or brain stem hemorrhage, traumatic/ or cerebral hemorrhage, traumatic/ or diffuse axonal injury/ or cerebrovascular trauma/ or craniocerebral trauma/ or contrecoup injury/ or epilepsy, post-traumatic/ or coma, post-head injury/ or head injuries, closed/ or head injuries, penetrating/ or intracranial hemorrhage, traumatic/ or hematoma, epidural, cranial/ or hematoma, subdural/ or hematoma, subdural, acute/ or hematoma, subdural, chronic/ or hematoma, subdural, intracranial/ or subarachnoid hemorrhage, traumatic/	49429
2	((TBI or sTBI or bTBI or ((trauma* or penetrat* or severe*) adj2 (brain or crania* or cranio* or cerebr* or cortex or head or skull)) or concuss* or postconcuss* or post-concuss*) not ("posttraumatic stress" or "post-traumatic" or PTSD)).ti,ab,kf.	71085
3	or/1-2	101693
4	limit 3 to (case reports or comment or editorial or letter or news)	19717
5	3 not 4	81976
6	Hypothermia, Induced/ or Cryotherapy/	24829
7	(hypotherm* or cool* or cold* or cryother* or cryogen* or cryotreat*).ti,ab,kf.	218524
8	or/6-7	224431
9	and/5,8	1518
10	limit 9 to yr="2014 -Current"	390
11	10 not ((animals/ not humans/) or (adolescen* or canine or child* or dog or dogs or mice or mouse or pediatri* or rat or rats or rattus or teen* or youth*).ti.)	272
12	limit 11 to (adaptive clinical trial or clinical trial, all or controlled clinical trial or equivalence trial or pragmatic clinical trial or randomized controlled trial)	31
13	limit 11 to (meta analysis or "systematic review")	13
14	or/12-13	44
15	11 not 14	228
16	exp Hyperventilation/	6446
17	(hyperventilat* or (ventilation adj3 therap)).ti,ab,kf.	8383
18	or/16-17	11261
19	and/5,18	484
20	limit 19 to yr="2014 -Current"	42
21	20 not ((animals/ not humans/) or (adolescen* or canine or child* or dog or dogs or mice or mouse or pediatri* or rat or rats or rattus or teen* or youth*).ti.)	33
22	limit 21 to (adaptive clinical trial or clinical trial, all or controlled clinical trial or equivalence trial or pragmatic clinical trial or randomized controlled trial)	2
23	limit 21 to (meta analysis or "systematic review")	0
24	or/22-23	2
25	21 not 24	31

#	Searches	Results
26	exp Barbiturates/	53485
27	(barbiturate* or pentobarb* or phenobarb* or methohexital* or thiamyl* or thiopental* or amobarb* or mephobarb* or barbital* or hexobarb* or murexide* or primidone* or secobarb* or thiobarb*).ti,ab,kf.	69792
28	or/26-27	90879
29	and/5,28	729
30	limit 29 to yr="2014 -Current"	76
31	30 not ((animals/ not humans/) or (adolescen* or canine or child* or dog or dogs or mice or mouse or pediatri* or rat or rats or rattus or teen* or youth*).ti.)	49
32	limit 31 to (adaptive clinical trial or clinical trial, all or controlled clinical trial or equivalence trial or pragmatic clinical trial or randomized controlled trial)	4
33	limit 31 to (meta analysis or "systematic review")	2
34	or/32-33	6
35	29 not 34	723
36	exp "Hypnotics and Sedatives"/	121054
37	(sedative* or Alprazolam or Amobarbital or Azaperone or Barbital or Bromisovalum or Chloral Hydrate or Chloralose or Chlordiazepoxide or Chlormethiazole or Dexmedetomidine or Diazepam or Diphenhydramine or Eszopiclone or Ethchlorvynol or Etomidate or Etorphine or Flurazepam or Glutethimide or Hexobarbital or Lorazepam or Medazepam or Medetomidine or Mephobarbital or Meprobamate or Methapyrilene or Methaqualone or Midazolam or Nitrazepam or Oxazepam or Paraldehyde or Pentobarbital or Phenobarbital or Propofol or Secobarbital or Temazepam or Thiamylal or Thiopental or Xylazine).ti,ab,kf.	129745
38	or/36-37	175276
39	and/5,38	950
40	limit 39 to yr="2014 -Current"	183
41	40 not ((animals/ not humans/) or (adolescen* or canine or child* or dog or dogs or mice or mouse or pediatri* or rat or rats or rattus or teen* or youth*).ti.)	122
42	limit 41 to (adaptive clinical trial or clinical trial, all or controlled clinical trial or equivalence trial or pragmatic clinical trial or randomized controlled trial)	10
43	limit 41 to (meta analysis or "systematic review")	5
44	or/42-43	15
45	41 not 44	107
46	exp Steroids/	837799
47	(steroid* or glucocorticoid* or prednisolone* or betamethasone* or cortisone* or dexamethasone* or hydrocortisone* or methylprednisolone* or prednisone* or triamcinolone* or corticosteroid*).ti,ab,kf.	473031
48	or/46-47	1084527
49	and/5,48	1790
50	limit 49 to yr="2014 -Current"	435
51	50 not ((animals/ not humans/) or (adolescen* or canine or child* or dog or dogs or mice or mouse or pediatri* or rat or rats or rattus or teen* or youth*).ti.)	294
52	limit 51 to (adaptive clinical trial or clinical trial, all or controlled clinical trial or equivalence trial or pragmatic clinical trial or randomized controlled trial)	27
53	limit 51 to (meta analysis or "systematic review")	16
54	or/52-53	43

#	Searches	Results
55	51 not 54	251



## Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
<b>1. Appropriateness</b>	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes
1b. Is the nomination a request for an evidence report?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
<b>2. Importance</b>	
2a. Represents a significant disease burden; large proportion of the population	High disease burden
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes - affects health care decision making, outcomes, or costs for a vulnerable population
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes – high associated costs to consumers, to patients, to health care systems, or to payers
<b>3. Desirability of a New Evidence Review/Absence of Duplication</b>	
3. A recent high-quality systematic review or other evidence review is not available on this topic	The only question with a recent high quality review is KQ3.
<b>4. Impact of a New Evidence Review</b>	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes. There is uncertainty about the role of various treatments in the management of severe TBI.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes, likely because of the clinical uncertainty.
<b>5. Primary Research</b>	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	We found 48 studies across 17 questions. Considering the distribution across the questions, a new review is not feasible.

**Abbreviations:** AHRQ=Agency for Healthcare Research and Quality;

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