SYSTEMATIC REVIEWS IN THE PRACTICE OF THE EPIDEMIOLOGY OF TRAUMATIC BRAIN INJURIES

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Abstract. High quality epidemiological data are vital for planning effective public health preventive strategies, providing health care services and evaluation of their effectiveness. Systematic reviews provide a summary of the results of carefully selected studies in a methodologically defined reproducible process. Authors of this article will present their experiences with the living systematic review of the epidemiology of traumatic brain injuries in Europe developed within the international project CENTER-TBI using the standardized methods.

Keywords: living systematic review, traumatic brain injuries, epidemiology, evidence-based medicine.

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Introduction

Systematic reviews by their nature provide a summary of the results of carefully selected studies in a methodologically defined reproducible process *(Elliott et al., 2014)*. The authors of this article will share their experiences in the use of systematic reviews for improving outcomes of patients after brain injury. The scientific value, form and how to perform systematic reviews, with examples for practice will form a part of this article.

Injuries are an important issue in public health and are one of the most common causes of mortality, especially in the group of young adults. Following cardiovascular, cerebrovascular, cancer and respiratory diseases, injuries are the fifth most common cause of death in the European Union *(European Commission, 2015)*. Traumatic brain injuries affect approximately 2.5 million people each year in Europe, and of these 1 million cases will lead to hospital admissions, and 75 000 deaths *(Maas et al., 2015)*.

Health research holds the potential of social benefits in the form of improved health. However, there has always been a certain gap between the results of research (evidence) and

health care practice *(WHO, 2005)*. Systematic reviews are important for bridging the gap from knowledge to practice by the synthesis of the high-quality evidences.

High quality epidemiological data are vital for planning effective public health preventive strategies, providing health care services and evaluation of their effectiveness *(Andelic, 2013; Koskinen and Alaranta, 2008; Popescu et al., 2015)*. There is a need to understand the patient-specific characteristics such as age, mechanism of injuries, and specific sensitive groups to reduce the occurrence of injuries in the society *(Leibson et al., 2011)*. The variations in data collection and analysis in population-based studies lead to the need to use standardized methods *(Maas et al., 2011; Menon and Maas, 2015; Menon et al., 2010)*.

Why systematic reviews?

The synthesis of complex, incomplete, and occasionally contradictory results of biomedical research into forms that can effectively orient health care professionals, in decision-making is a basic component of the bridge between theory and practice *(Elliott et al., 2014; Sackett et al., 1996)*. Systematic reviews are key stages for evidence-based health care. The need to perform them before generating new data is highlighted by several international groups. One example is EBRNetwork, which directly encourages researchers to reduce waste of research, and this network helps to clarify an evidence-based approach through numerous available sources of information and news *(EBRN, 2018)*.

The beginnings of systematic reviews date back to 1753 when James Lind, a Scottish naval surgeon, presented a critical and chronological view of his previously published information about scurvy in his famous treatise *(Lind, 1753)*. This summary of the diverse nature of the research results remains an important task of systematic reviews. Moreover, systematic reviews are generally recognized as the most reliable source of research findings *(Ioannidis et al., 2014)*. Their position is at the top of the evidence hierarchy *(Murad et al., 2016)*. They are also key to clinical and policy guidelines published by international organizations such as the World Health Organization *(WHO, 2014)*.

The ultimate aim of the article is to describe procedures of incorporating the systematic reviews into scientific exploration of factors, which may lead to improved understanding of risk factors, higher-risk groups, and outcomes of people following brain injury.

Methodology

Synthesis of Evidences

The team of Trnava University has gained experience in conducting systematic reviews of epidemiology of traumatic brain injuries (TBI) in Europe *(Brazinova et al., 2016)*. This work was carried out within the CENTER-TBI (Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury) project, a multi-centre study involving 38 organizations from Europe and USA *(CENTER-TBI, 2018)*. A team of experts from Trnava University has long been involved in comprehensive research on epidemiology of traumatic brain injuries in Europe and conducting systematic reviews *(Rehorčíková et al., 2016)*. This team cooperates with partners from Australia's Monash University and follows the gold-standard Cochrane Collaboration guidelines. Cochrane Collaboration is a recognized

international non-profit organization that creates, supports and disseminates systematic reviews and meta-analyses about the effectiveness of the healthcare interventions *(COCHRANE, 2018a)*.

In compliance with generally accepted methodology our team started designing progressive work plan - a protocol before performing each systematic review *(Synnot et al., 2016)*. We made use of the protocol writing procedure PRISMA *Preferred Reporting System for Systematic Reviews and Meta-Analyses*. PRISMA represents a checklist that consists of 27 items that relate to the process of developing individual parts of a systematic overview and a flowchart. This flowchart illustrates the process of studies selection *(Moher et al., 2009)*. Protocols are then registered in the international databases. Examples are the Cochrane protocols published in the Cochrane library *(COCHRANE, 2018b)*, as well as the international PROSPERO registered protocols database *(NIHR, 2018)*. These databases are primarily created to provide an overview of the systematic reviews that will result in the retrospective compliance with the stated objectives in the protocol and avoid duplication.

The protocol must include all steps to be taken when preparing a systematic review *(Synnot et al., 2016)*:

- Search for relevant studies within the electronic databases in which the search will be carried out, using pre-specified keywords and search algorithms.
- The screening process and the inclusion/exclusion criteria.
- Assessment of the methodological quality of studies to the identified research question.
- Data synthesis from included studies.

For reporting of systematic reviews developed in this project we followed IMRaD (Introduction, Methods, Results, and Discussion) structure. The first phase of the process was the identification of the study. Using search algorithms that consisted of keywords entered to the bibliographic databases (such as PubMed, Embase, Cinahl), a longlist of studies was acquired. At this stage, we removed possible duplicates that were created by searching multiple databases using the same keywords. Then, the phase of title- and abstract-screening of all the studies identified in the first phase began. Evaluators from our team, based on well-defined inclusion and exclusion criteria, selected abstracts as the basis for moving to the next stage. Finally, the full text screening of those studies where abstracts were selected in the previous phase was performed. Whenever possible we used another independent evaluator, other than those evaluating the inclusion of abstracts, performing this activity. As a result, only those studies that met the specified selection criteria were included to the final set of studies. These were included into a systematic review and were ready for use or publication.

A detailed overview of all of the included studies (design, population, studied period, data sources, definitions and number of cases) should be presented in any systematic review. Another important part is the description of the methodological quality assessment of the studies. The aim is to eliminate those studies with systematic errors or misleading factors *(Synnot et al., 2016).* There are various tools available for this rating process. One of them is the MORE checklist (Methodological evaluation of Observational REsearch) *(Shamliyan et al., 2011)*. These tools help to evaluate the validity of the study, i.e. whether the methodological deficiencies are present or absent in the design of studies, in data collection, data analysis. The studies quality assessment should be carried out by two independent authors of the systematic review.

Data from the individual studies can be synthesized in a descriptive way – using tables, or by using statistical methods – meta-analysis. Performing meta-analysis is potentially

useful, because the combined population size of the individual studies increases the total sample size. This will increase the statistical strength of the analysis as well as the precision of the effect estimation *(Akobeng, 2005; Clarke and Chalmers, 2018).* However, such analyses can only be fairly performed if the studies of the original studies, which contribute data to the analysis, are sufficiently similar. The meta-analysis consists of two phases. The first step involves calculating the effect size with 95% confidence intervals (CI 95%) for each individual study.

In the second phase, the total efficacy effect is calculated in the form of a weighted average of the individual summary statistics. An important fact is that in meta-analysis data from the individual studies are not combined as if they were from one study. Higher weights are attributable to the studies that provide more information and are likely to be closer to the "true effect" *(Akobeng, 2005)*.

New form of the systematic reviews

Recently, a new variation called “living” systematic reviews is available as a form of systematic review. The basic difference between these new “living” versions and conventional systematic reviews is the format of the publication. “Living” systematic reviews are dynamic summaries of the evidences and are available online only. They are unique by being regularly updated (for example once every 3 to 6 months) with the results of the new studies *(Elliott et al., 2014)*.

Results

Authors of this article have developed the systematic review of epidemiology of traumatic brain injuries in Europe, which is an example of a “living” systematic review *(Brazinova et al., 2018)* and are publishing its updates as online supplementary material in the Journal of Neurotrauma. This Trnava University team within the project CENTER-TBI participates in the Living Evidence Network (LEN) led by the representativeness from the Monash University in Australia *(Cochrane Community, 2018)*. The LEN is an informal network with members including Cochrane and non-Cochrane researchers, policymakers and guideline developers and includes 5 Interest Groups:

1. Search.
2. Technology.
3. Methods.
4. Publication.
5. Knowledge translation and stakeholder engagement.

Interest Groups are designed for information-sharing for the many LEN members who are keen to stay abreast of developments in their field and to facilitate ad hoc discussion on topics relevant to the Interest Group *(Cochrane Community, 2018).*

The process of doing updates is a very similar to the original systematic review and is performed in a standardised way. The example of the process of the first update developed by the authors of this article is presented in the Figure 1.

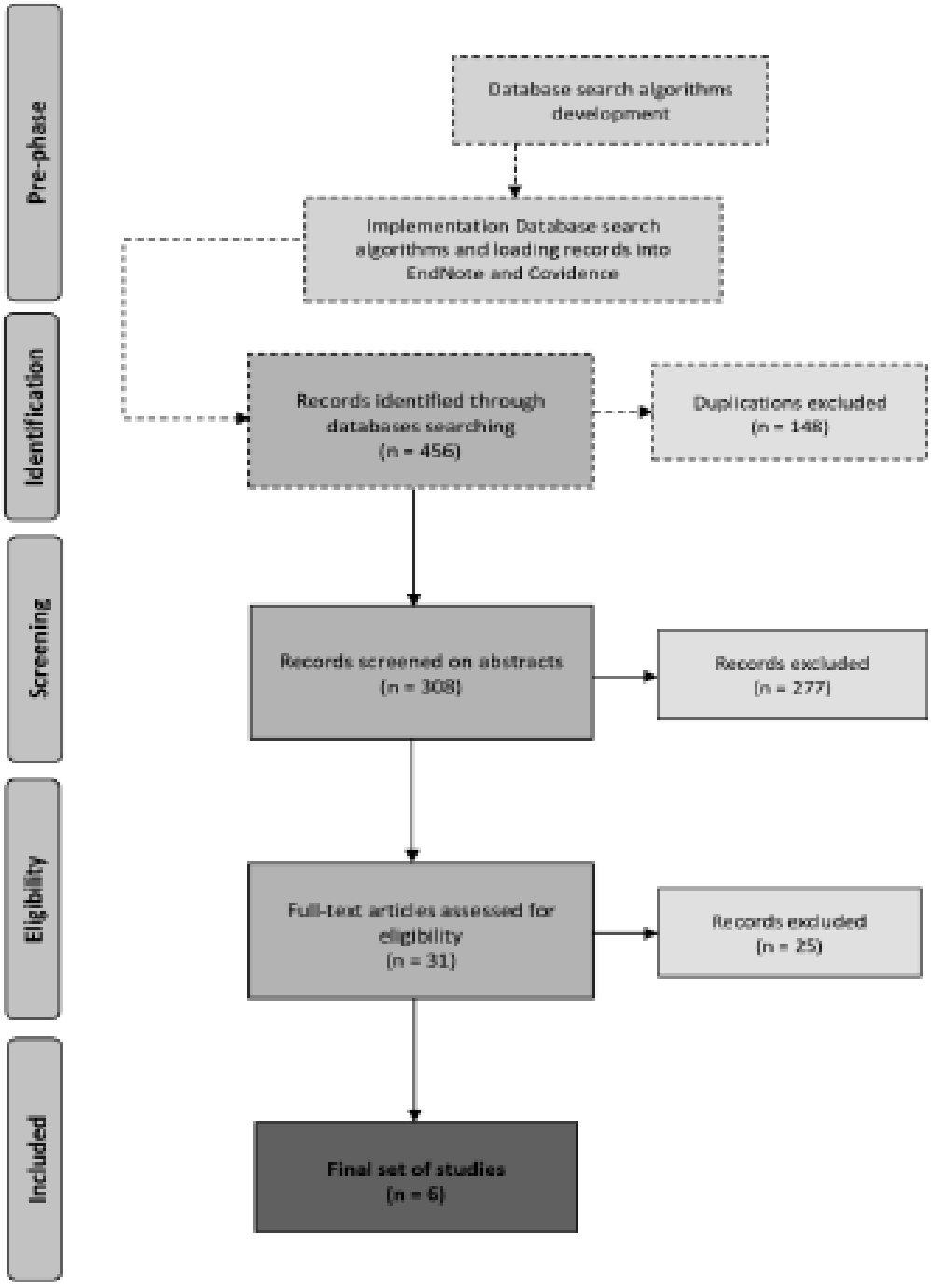

Fig. 1. The process of developing the "living" part of the systematic review

One difference is in the method of searching for new records - re-running search. This means that the results of the databases are again searched and the date of the last search is very important for the other update. This is performed by the re-creating the database search algorithms with the new dates or using the databases' automatic alerts of newly published studies. Within this pre-phase there is a need for careful management of the whole screening process. The authors of this living systematic review are using the managing toolkit of the Cochrane's review production – Covidence *(COVIDENCE, 2018)*.

Other steps in the development of a living-systematic review, such as abstracts and full-text papers screening, assessment of the methodological quality of included studies are performed by a standardised process as in any original systematic review. Data synthesis is performed by the combination of new results with anything previously published.

A table with the search dates, number of newly included studies and with implications for practice is very helpful as an overview of the new results, within the living part of the original systematic review, Figure 2.

Version	*Search date*	*No. new included studies*	*Implications for conclusions*
Original	January 2015	66	n/a
Update 1	February 2016	This update: 6 Cumulative for updates: 6	unchanged
Update 2	March 2017	This update: 4* Cumulative for updates: 10	Wider range of national incidence rates
Update 3	November 2017	This update: 6* Cumulative for updates: 16	First pooled results from multi-national studies
Update 4**	August 2018	This update: 2 Cumulative for updates: 18	Highest national incidence, (although we note wide inclusion criteria)

*Two studies that have previously been mentioned as showing mechanisms of injury, have since been deemed ineligible as they did not publish any rates.

**A review of the search strategy was undertaken prior to the August 2018 search. See Appendix S1 for details.

Fig. 2. Example of living systematic review history *(Brazinova et al., Suppl. 2018)*

As in the original systematic review, the Methodological quality of the newly included studies in the living updates is assessed using the MORE checklist (Methodological Evaluation of Observational REsearch) *(Shamliyan et al., 2011)*. Studies are not excluded from the review according to their methodological quality, but the rigour of reported design is described in the textual summary of results. The assessed domains with the proportions of their scored criteria such as: general descriptive elements, external validity, internal validity and reporting of the estimates are presented in the Figure 3, as the example of their assessment *(Brazinova et al., Suppl. 2018)*.

Discussion

Incorporating systematic reviews into research and clinical practice, may be limited by the fact that there is no such review in the given area, or that previous systematic reviews are obsolete. This leads to opportunities for research teams that are specialized in performing such reviews and publishing the results.

	OK *n* (%)	*Minor flaws* *n* (%)	*Major flaws* *n* (%)	*Poor reporting* *n* (%)	*NA* *n* (%)
General descriptive elements					
Aim of study	13 (72)	1 (6)	1 (6)	2 (11)	1 (6)
Funding of study	13 (72)	0	0	5 (28)	0
Conflict of interest	17 (94)	0	0	1 (6)	0
Ethical approval	11 (61)	0	0	7 (39)	0
Study design	13 (72)	0	0	5 (28)	0
External validity					
Sampling	10 (56)	8 (44)	0	0	0
Definition of cases					
• Validation	11 (61)	2 (11)	4 (22)	1 (6)	0
• Severity of TBI	8 (44)	2 (11)	3 (17)	3 (17)	2 (11)
Sampling bias	10 (56)	1 (6)	1 (6)	4 (22)	2 (11)
Subject flow	17 (94)	0	0	0	1 (6)
Internal validity					
Reporting of methods					
• Source of data	10 (56)	8 (44)	0	0	0
• Reliability of estimates	15 (83)	1 (6)	0	2 (11)	0
Reporting of estimates					
Incidence*					
• Incidence type	7 (78)	2 (22)	0	0	0
• Precision of estimation	6 (67)	1 (11)	2 (22)	0	0
• Type of incidence rate in total sample	3 (33)	5 (56)	0	1 (11)	0
• Type of incidence rate in subgroups	3 (33)	4 (44)	0	2 (22)	0
Mortality**					
• Mortality type	4 (27)	2 (13)	9 (60)	0	0
• Precision of estimation	3 (20)	2 (13)	10 (67)	0	0
• Type of mortality rate in total sample	3 (20)	2 (13)	1 (7)	0	9 (60)
• Type of mortality rate in subgroups	4 (27)	1 (7)	1 (7)	0	9 (60)

MORE, Methodological Evaluation of Observational Research checklist; TBI, traumatic brain injury; *reported in 9 studies; **reported in 15 studies

Fig. 3. Quality assessment of the studies included in the living part of the original systematic review using MORE checklist *(Brazinova et al., Suppl. 2018)*

Systematic review preparation is a complicated process, and depends on the type of clinical studies that are available, how they were performed (the quality of the studies), and which health outcomes were processed. We have produced the most up-to-date and complete review of TBI epidemiology across Europe. The methods used in this review were standardized and well described.

Not all systematic reviews should have this "living" approach. The LSRs are important if the systematic review is necessary for decision-making and allocation of sources, the existing evidence is a low quality and uncertain, current information can change the previous findings, new evidence is emerging *(Elliott et al., 2017)*.

The systematic reviews are as good as the primary data sources are. This is the reason why each study included in a systematic review should be assessed for its quality. It is important, that the authors of the high quality systematic reviews report the methods used for bias assessment *(Drucker, Fleming and Chan, 2016)*. However, bias can occur in any stage of the review process. The potential bias of the systematic review should be stated for the users when interpreting the results and conclusions *(Whiting et al., 2016)*.

Authors of systematic reviews must take all possible steps to prevent potential biases. The Cochrane Collaboration guidelines *(Higgins et al., 2016)* and US Institute of Medicine standards *(Eden et al., 2011)*, the PRISMA statement *(Moher et al., 2009)* help to minimize bias in the systematic review development. The Trnava University team presented several limitations to their LSR on epidemiology of TBI in Europe. These limitations were related to the case ascertainment and definitions of TBI, different TBI reporting procedures and

practices across Europe, the methods used to ascertain the mechanism of injuries in the included studies (*Brazinova et al., 2016)*.

Conclusions

The authors recommend that systematic reviews should take their place in the practice of health care professionals, and the compilation and comprehension of such documents should be an important competency of both academic and clinical staff. The Department of Public Health of Trnava University has demonstrated its expertise in the international project CENTER-TBI and offers cooperation in similar activities.

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