DEVELOPMENT OF EVIDENCE-BASED PRACTICE GUIDELINES AND SYSTEMATIC REVIEWS: METHODOLOGICAL CHARTER

by the Centre for Evidence-Based Practice (CEBaP)
of the Belgian Red Cross

About the Centre for Evidence-Based Practice (CEBaP)

The Centre for Evidence-Based Practice (CEBaP) is a non-profit global centre located in Belgium that supports humanitarian and development aid activities, including those of Belgian Red Cross, with scientific evidence. The CEBaP researchers work on a daily basis on the development of systematic reviews, evidence-based guidelines and primary field research, relevant to the aid sector.

More information on CEBaP can be found on:

- The CEBaP website;
- CEBaP's Twitter account (@CEBaP_evidence);
- CEBaP's LinkedIn Company Page.

About this charter

This charter aims to shed some light on CEBaP's day-to-day functioning, with a clear emphasis on the rigorously performed and transparently reported systematic literature searches. More specifically:

- In the first part of this charter, the methodological standards used by CEBaP during the development of evidence-based guidelines (according to AGREE II) and systematic reviews (following the Cochrane methodology) are described in detail.
- In a second part, more information is provided on the initiation and further flow of the guideline and review projects co-developed by CEBaP.

If the necessary resources (e.g. funding, time) for the development of a systematic review or guideline are insufficiently available, deviations from the methodology described in part one of this charter may occur and will be discussed with the CEBaP Steering Committee (see part two).

Should you still have questions after reading this charter, do not hesitate to contact the CEBaP researchers via info@cebap.org.

Table of content

PART 1: CEBAP'S METHODOLOGICAL STANDARDS

A) EVIDENCE-BASED PRACTICE GUIDELINES

1. What is an evidence-based practice guideline?

A practice guideline consists of a set of recommendations, advice and instructions that aim to support good practice and guide decision-making in the field.
In order to qualify as "evidence-based", the guideline should be developed in such a way that it becomes informed by all three pillars of Evidence-Based Practice:

1) The best available scientific evidence;
2) The practical experience and expertise of experts in the field;
3) The preferences and available resources of the target group.

This short video depicts how a combination of these 3 pillars results in an evidence-based recommendation in the context of a practice guideline.

2. How is an evidence-based practice guideline developed by CEBaP?

During the development of evidence-based practice guidelines, CEBaP adheres to the AGREE II instrument, which is the current gold standard used by guideline developers.[1]
The purpose of the 23-item AGREE II tool is:

1) To enable quality appraisal of guidelines;
2) To provide a methodological strategy for the development of guidelines
3) To describe what information ought to be reported in a guideline and in which format.

In agreement with the Evidence-Based Practice triangle, CEBaP starts off with a systematic literature search in order to identify the best available scientific evidence to back up the recommendations. This evidence is then presented to and discussed by a panel of experts. The experts decide whether or not to recommend certain interventions, taking into account the quality of the evidence, the feasibility, the benefits and harms of the intervention, and the costs. In addition, the preferences of the target population are taken into account as well. The final recommendations are therefore the result of a thorough process that combines scientific evidence with expert opinion and target group preferences.

During the development of evidence-based practice guidelines, CEBaP adheres to all 23 items of the AGREE II instrument. In the following paragraphs, we elaborate further on how CEBaP addresses 10 of those that leave most room for interpretation.

2.1 The health questions covered by the guideline are specifically described (item 2)

At the start of the guideline development phase, CEBaP meets with the guideline-requesting party (most of the times a Belgian Red Cross service) in order to draw up a list of clearly defined questions that should be covered by the guideline.
Questions that require the conduct of systematic literature searches are converted to questions that precisely define the **P**opulation, **I**ntervention, **C**omparison and **O**utcome of interest (PICO questions).

Depending on the type and scale of the guideline project, certain criteria are set in considering whether questions should be converted to PICO questions or not.
In general, during the development of evidence-based guidelines for laypeople of the Belgian Red Cross, no systematic literature searches are started when the intervention of interest concerns:

- A 'Good Practice Point' (i.e. short pieces of advice which may not have an evidence base, but which are seen as essential to good clinical practice [2]) or common sense;
- The responsibility of professionals (such as a medical doctor or pharmacist);
- Interventions with only a long-term effect (e.g. lifestyle interventions such as healthy diet, smoking cessation);

- The practical organisation of activities (e.g. use of EpiPen);
- (Medico-)legal aspects;
- Anatomy or physiology.

Similarly, no PICO questions are formulated if the risk factor of interest:

- does not precede the outcome;
- is common sense;
- is a fixed marker (e.g. race, gender);
- is a distal risk factor (e.g. smoking as a risk factor for lung cancer);

2.2 The guideline development group includes individuals from all relevant professional groups (item 4)

The guideline development group consists of:

- the members of the Steering Committee of CEBaP;
- the CEBaP researcher(s) responsible for collecting the evidence;
- the Belgian Red Cross service or the external party for whom the guideline is being developed and that is responsible for writing the draft recommendations;
- an expert panel that makes a trade-off between the quality of the evidence, benefits and harms, and validates the final recommendations.
  This multidisciplinary expert panel consists of a chairman, who has the necessary expertise in evidence-based methodology and in the content of the project, and additional panel members, who at a minimum have expertise in the content of the project.

2.3 The views and preferences of the target population have been sought (item 5)

The guideline development group receives information about the views and preferences of the target population from one or more of the following:

- the Belgian Red Cross service involved, which has expertise in the content or collects the necessary information (e.g. by composing a reading group or by interviewing the target population);
- a literature search concerning the values, preferences and experiences of the target population;
- a feedback round or pilot test.

In addition, the target population is also included in the guideline development group.

2.4 Systematic methods are used to search for evidence (item 7)

The AGREE II instrument does not provide a detailed description of the methodology that should be used during the literature search. Hence, CEBaP has based its methodology on the ones used by two of the leading guideline development organizations, i.e. the Scottish Intercollegiate Guidelines Network (SIGN) and the National Institute for Health and Clinical Excellence (NICE).

Since an evidence-based practice guideline often covers a myriad of different topics, CEBaP adopts a pragmatic approach to its systematic literature searches, to ensure that the development of the practice guideline is feasible within a reasonable time span (in line with the SIGN methodology).
To this end:

- for each PICO question, CEBaP designs a specific (*i.e.* not a sensitive or exhaustive) search strategy for a limited number of databases;
- this search strategy is developed by a single reviewer and evaluated by a second reviewer;
- the selection, quality appraisal and synthesis of the relevant evidence is performed by a single reviewer.

For the sake of reproducibility and transparency, the entire systematic search process is rigorously documented by the CEBaP reviewer in an **evidence summary**, using the template presented in **Appendix 1**.

Evidence sources

By default, CEBaP searches the following electronic databases to identify potentially relevant systematic reviews and individual (experimental and/or observational) studies:

- The Cochrane Library, including the following databases:
  - Central Register of Controlled Trials (CENTRAL);
  - The Cochrane Database of Systematic Reviews.
- MEDLINE (via PubMed interface);
- Embase (via Embase.com interface).

Depending on the guideline topic, additional/other databases that might contain relevant evidence may be included (e.g. Web of Science, CINAHL, ERIC, PsycNet).

In addition, the reference lists of included references (i.e. those that meet the selection criteria, see 2.5) that were retrieved using the initial search, are scanned for additional relevant references. Also, if available, the "Related Articles" feature of the databases is used; if the included article is registered in MEDLINE, the first 20 related citations are scanned.

No efforts are made to retrieve grey literature, unless this is required for a specific project.

Search terms

A specific search string is tailored to each database and comprises both index terms (if relevant; e.g. MeSH terms, Emtree terms) and free text words (in title or abstract), with attention to possible synonyms, spelling variants, and correct use of truncation and proximity operators.

Search filters

In general, CEBaP tries to use search filters judiciously, only when they are considered to have added value, e.g. for the sake of feasibility when the number of records to screen is large, as they may prevent the retrieval of relevant papers.

Search period

By default, databases are searched from their date of inception until present. However, in the context of a guideline update, for pre-existing PICOs, search periods are adapted to ensure that the time period of the new search overlaps that of the previous one by at least 2 months.

2.5 The criteria for selecting the evidence are clearly described (item 8)

A clear set of selection criteria is determined by the CEBaP reviewer. These criteria are as specific as possible and generally do not allow the inclusion of indirect evidence. They include criteria related to the population, intervention, comparison, outcomes, study design, publication type and publication language.

Study design

As for study design, CEBaP generally applies the following criteria:

- *Include:* a systematic review: inclusion of a systematic review as a whole if the search strategy and selection criteria are clearly described and if at least 3 relevant databases are searched. Inclusion of a systematic review as a source of studies if the search strategy and selection criteria are clearly described and at least two relevant databases have been searched.
  An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial (RCT), and the data are available.
  An observational study: inclusion in case of one of the following study types: cohort and case-control study, controlled before and after study or controlled interrupted time series, and the data are available.
- *Exclude:* case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values.

However, depending on the project and context, these criteria can be altered.

For example:

- If the evidence base is limited or even non-existent when only including the above study designs, it can be decided to expand these criteria and also include observational cross-sectional studies;
- If there is a sufficient amount of high-quality research (e.g. systematic reviews of RCTs, RCTs), CEBaP can opt to exclude other lower-quality observational studies.

In these cases, the CEBaP reviewer provides a rationale in the In-/Exclusion criteria section of the **evidence summary** (**Appendix 1**).

Publication types

Articles that are published in a peer-reviewed journal are included. Conference abstracts, conference papers, (clinical) trial registrations, letters to the editor and dissertations are excluded, as they are generally not subjected to peer review.

Publication language

By default, CEBaP only selects articles published in English. Depending on the project, additional publication languages may be included as well.

These selection criteria are documented in the In/Exclusion criteria section of the **evidence summary** (**Appendix 1**).

On the basis of these criteria, study selection is performed by a single CEBaP reviewer. In a first phase, titles and abstracts of the references identified by the search are screened. Full texts of potentially relevant papers are retrieved, and references that meet the selection criteria are included.

2.6 The strengths and limitations of the body of evidence are clearly described (item 9)

In a next phase, the CEBaP reviewer assesses the methodological quality and potential shortcomings therein for all the included individual studies. To this end, the key criteria set by the GRADE approach are utilized.[3] According to this approach, the following study limitations are likely to result in biased results ("risk of bias"):

- Experimental studies:
    - Lack of allocation concealment;
    - Lack of blinding;
    - Incomplete accounting of patients and outcome events;
    - Selective outcome reporting;
    - Other limitations.

- Observational studies:
    - Failure to develop and apply appropriate eligibility criteria;

- Flawed measurement of both exposure and outcome;
- Failure to adequately control confounding;
- Incomplete or inadequately short follow-up.

For other study types that require a specific quality appraisal tool, the appropriate formal tool is used to evaluate the risk of bias and possible other aspects, such as applicability (e.g. QUADAS-2 tool for primary diagnostic accuracy studies).

Next, the GRADE approach is used to assess the overall certainty of the evidence included, based on the study limitations, imprecision, inconsistency, indirectness, and publication bias.[4] The certainty of the body of evidence is assigned, ranging from high, moderate, low to very low.

Based on the study findings, the CEBaP reviewer writes an evidence conclusion. **The wording used for the evidence conclusion** depends on the certainty of the evidence and the (im)precision of the study findings.

2.7 The methods for formulating the recommendations are clearly described (item 10)

On the basis of the conclusions made in the evidence summaries, preliminary recommendations are drafted by content experts (e.g. employees of the Belgian Red Cross service for whom the guideline is being developed, or external content writers). Both the evidence summaries and these draft recommendations are provided to the multidisciplinary expert panel (see 2.2).

The expert panel goes through the evidence summaries and the draft recommendations, checks if the recommendations are consistent with daily practice, and discusses additional considerations (see 2.8) that should inform the final recommendation.
If the panel decides to reformulate a recommendation, informal methods are used to reach consensus on the final recommendation. If consensus cannot be reached, the decision is made through majority voting.

2.8 The health benefits, side effects, and risks have been considered in formulating the recommendations (item 11)

Before formulating the final recommendations, the expert panel has to discuss the following questions:

- Are we confident that the possible benefits outweigh the harms and burdens of the recommended intervention?
- What is the overall certainty of the evidence? How confident are we?
- Are we confident about the values and preferences of the target population?
- Are the required resources worth the expected net benefit from the recommendation?

Based on these considerations, the expert panel decides on the strength of recommendation (i.e. strong or weak), defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects.

2.9 The guideline has been externally reviewed by experts prior to its publication (item 13)

Before finalising the guideline, it is reviewed by external experts who have not been involved in the guideline development. If possible, representatives of the target group are also part of the external reviewing team.

2.10 A procedure for updating the guideline is provided (item 14)

An evidence-based practice guideline is updated every 5 years, if funding is available and capacity allows it.

For each evidence summary that is developed to support an evidence-based practice guideline, the necessity to update is assessed after its development. Situations in which an evidence summary may be declared stable include:

- The conclusion is so certain that the addition of new information will not change it, and there are no foreseeable adverse effects of the intervention (conclusive evidence);
- The intervention can now be considered common sense and the evidence supports the recommendation.

3. Where can I consult the evidence-based practice guidelines and the underlying evidence summarized by CEBaP?

3.1 Evidence-based practice guidelines

Full guidelines

A number of evidence-based guidelines that have been co-developed by CEBaP have been made fully available to the public. Examples are:

- The Belgian Red Cross First Aid guideline for laypeople (Help! First aid for everyone);
- The Belgian Red Cross African First Aid Materials;
- The Belgian Red Cross educational pathway on first aid for sub-Saharan Africa.

Peer-reviewed publications on guideline development

Publications that describe the process and results of some specific guidelines can be accessed via the Publications section of our website.

3.2 Evidence summary database

As mentioned before, each systematic literature search that is performed by CEBaP is rigorously and transparently documented, using the evidence summary template.

All evidence summaries are internally archived in the online evidence summary database on the CEBaP project site (developed in Sharepoint). This database ensures rapid document retrieval and offers the ability for future database enhancement.

The summaries that are developed in the context of first aid guideline development are made publicly available and can be consulted in our external First Aid Evidence Summary Database. Access to this database is free, but requires registration. New evidence summaries and updates of existing ones are regularly added.

B) SYSTEMATIC REVIEWS

1. What is a systematic review?

A systematic review gives an overview of the best available scientific evidence on a very specific topic or question. A systematic review can be used to inform policy-making, or can serve as evidence to inform recommendations made in an evidence-based guideline.

Unlike an evidence-based guideline, a systematic review does not take into account expert opinion or target group preferences, nor does it contain any recommendations. However, in the Discussion section of a systematic review publication, suggestions can be made on potential implications for practice by highlighting different possible actions. In addition, the implications for research can be discussed.

2. How is a systematic review developed by CEBaP?

When it comes to the term 'systematic review', semantics are of the essence: a systematic review literally means 'performing a literature review in a systematic way'. If you were to compare 5 randomly chosen peer-reviewed publications that call themselves a 'systematic review', you may notice that all 5 reviews have used a different (though systematic) approach to the literature review. In other words, systematic reviews can be developed in accordance with different methodological standards.

Systematic reviews by CEBaP are always developed according to the most strict and rigorous methodological principles of Cochrane, as described in the Cochrane Handbook for Systematic Reviews of Interventions.
As a consequence, the methodology used by CEBaP during the development of a systematic review displays quite a number of differences compared to that used during guideline development (see Table 1).
Exceptions are scoping reviews or scoping exercises. As these are not specifically mentioned in the Cochrane Handbook, and there are some deviations from the standard methodology, CEBaP uses its self-developed guidance (based on chapter 11 of the JBI manual for evidence synthesis[9]) and the PRISMA extension for scoping reviews[10]) on how to perform these types of reviews.

In general, CEBaP focuses on the development of systematic reviews of quantitative studies. Depending on the type of project and the requesting party, a mixed-methods review (including both quantitative and qualitative studies) may be considered.

Table 1: Differences in methodological principles applied during the development of an evidence-based practice guideline versus a systematic review by CEBaP

Methodological principle	Evidence-based practice guideline	Systematic review
Protocol development	No	Yes
Number of reviewers • Developing search strategy • Performing literature search and article selection • Performing data extraction • Performing quality appraisal	 • 1 reviewer, but checked by 2nd reviewer • 1 reviewer • 1 reviewer • 1 reviewer	 • 1 reviewer, but checked by 2nd reviewer • 2 independent reviewers • 2 independent reviewers • 2 independent reviewers
Selection criteria related to study design	Systematic reviews, experimental studies and/or observational studies. The CEBaP reviewer may adjust these criteria during the review process, depending on the quality and amount of available evidence.	Experimental studies and/or observational studies. The CEBaP reviewers consider a priori what study designs are likely to provide reliable data with which to address the objectives of the review.
Selection criteria related to Population, Intervention, Comparison and Outcome	The CEBaP reviewer sets narrow criteria that may be redefined during the review process, depending on the amount of available evidence.	The CEBaP reviewers use comprehensive, a priori criteria.
Evidence sources	The Cochrane Library, MEDLINE, Embase (and/or other sources relevant to the guideline topic). No efforts are made to identify grey literature.	At a minimum: The Cochrane Library, MEDLINE, Embase. Depending on the project, efforts are made to identify grey literature.
Search strategy	Specific search string	Sensitive search string
Quality appraisal	Per intervention	Per outcome
Expert panel input	Yes, via expert panel	Yes, at least 1 content expert
Formulating recommendations	Yes	No
Assessment of the strength of recommendation	Yes	No

In the following paragraphs, we highlight how the systematic literature search for a systematic review by CEBaP differs from that conducted in the context of guideline development.

2.1 Protocol development

In the context of a new systematic review, a protocol is developed in which the review scope and methods are specified *a priori*. This helps to reduce the risk of bias in the review process and maximises transparency and accountability.
The actual systematic review process can only start after the protocol is registered or published, e.g.:

- In the PROSPERO register of systematic reviews;
- In the Registered Reports publishing format;
- In a peer-reviewed journal;
- On a pre-print server (e.g. medRxiv);
- On the CEBaP website.

2.2 Criteria for considering studies

PICO question and criteria

Two CEBaP researchers acting as independent evidence reviewers for the systematic review will sit down together to formulate the PICO question.
Together, the reviewers also determine and document the criteria for the population, intervention, comparison and outcomes of interest in a clear and unambiguous manner. The reviewers may choose to divide the outcomes into primary (considered most important) and secondary outcomes. If so, they indicate this clearly in the selection criteria.

Study design

In addition, the types of study design that will be considered for including studies into the review are clearly specified. In making this choice, the CEBaP reviewers consider a priori which study design types are most likely to contain the bulk of the evidence concerning the PICO question.

Publication types

In general, peer-reviewed journal articles, conference abstracts, conference papers, (clinical) trial registrations, letters to the editor and dissertations are included.

Publication language

By default, all publication languages are included.

2.3 Search methods for identification of studies

Evidence sources

At a minimum, the following electronic databases are searched:

- The Cochrane Library, including the following databases:
  - Central Register of Controlled Trials (CENTRAL);
  - The Cochrane Database of Systematic Reviews.
- MEDLINE (via PubMed interface);
- Embase (via Embase.com interface).

Depending on the systematic review topic, additional databases that potentially contain relevant evidence may be included (e.g. Web of Science, CINAHL, ERIC, PsycNet).

In contrast to during guideline development, efforts are made to retrieve grey literature. To this end, grey literature repositories, trial registries and/or conference proceedings are searched as well. Depending on the topic of the review, these sources may include:

- Grey Literature Report (www.greylit.org);
- OpenGrey (www.opengrey.eu);
- Google Scholar (scholar.google.com);
- ClinicalTrials.gov (clinicaltrials.gov);
- EU Clinical Trials Register (www.clinicaltrialsregister.eu)
- WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/);
- ISI Web of Science Conference Proceedings Citation Index-Science (CPCI-S) (https://www.webofknowledge.com).

When preparing a Cochrane review, we closely cooperate with the Trials Search Co-ordinator of the corresponding Cochrane Review Group in the search for studies.

Similar to during guideline development, the reference lists of included references (i.e. those that meet the selection criteria) are scanned for additional relevant references. However, in contrast to guideline development, if the reference list of a paper, retrieved using the initial search, reveals an additional eligible article, the reference list of this newly included reference is also scanned (snowballing technique).

Search terms

In contrast to the specific search string used during guideline development, a very sensitive search string is elaborated during the search for evidence for a systematic review.

Search filters

Search filters may prevent the retrieval of relevant papers and therefore undermine the essential comprehensive character of a systematic review. However, if the systematic reviewers

do decide to use any filters, they transparently report this in the search strategy and explain the rationale.

Search period

In the context of a new systematic review, databases are searched from their date of inception until present, unless a substantiated rationale is available for focussing on a specific time window.

In the context of a systematic review update, search periods are adapted to ensure that the time period of the new search overlaps that of the previous one by at least 2 months.

2.4 Data collection and analysis

Study selection, data extraction and management, and assessment of risk of bias in the included studies is always performed by 2 independent reviewers. Any discrepancies between the 2 reviewers are resolved through discussion. If they fail to reach consensus, a third reviewer is consulted.

Study selection

Study selection is performed by 2 independent reviewers.

Data extraction and management

The two CEBaP reviewers independently extract data from all included studies using the evidence summary template.

Assessment of risk of bias in included studies

Individual studies are assessed for risk of bias, independently by the two reviewers.

In the context of a Cochrane systematic review, the Cochrane Risk of Bias 2 tool is used to identify the methodological quality and potential shortcomings of randomized controlled trials.[5] In this tool, assessments are made within the domains of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data addressed, selective reporting and possible other bias. Each domain is rated as being at low, high or unclear risk of bias.

Study quality of non-randomized experimental and observational studies is assessed using the Risk of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool.[6]

During the development of other (non-Cochrane) systematic reviews, the CEBaP reviewers use the key criteria set by the GRADE approach to assess the methodological quality and potential shortcomings therein for all the included individual studies.[3]

For both Cochrane and non-Cochrane systematic reviews, the overall certainty of the "body of evidence" is determined independently by the two reviewers through use of the GRADE

approach, based on the limitations in study design (risk of bias), imprecision, inconsistency, indirectness, and publication bias.[4]

Dealing with missing data

In case of missing data, the CEBaP reviewers attempt to contact the study authors, in order to obtain these data.

If possible, missing values are calculated from the available data (e.g. P values, t values, CIs or standard errors). If insufficient data are available to calculate missing values, CEBaP only analyses the available data.

Assessment of heterogeneity

Heterogeneity between studies is determined and addressed according to the guidance in the Cochrane Handbook for Systematic Reviews of Interventions.

Assessment of publication bias

In agreement with the Cochrane Handbook for Systematic Reviews of Interventions, if 10 or more studies are identified, publication bias is assessed through visual inspection of funnel plots. If the funnel plot shows asymmetry, the reviewers perform appropriate formal statistical tests.

Data synthesis

Experimental and observational studies are always analysed separately by the reviewers. If 2 or more studies investigating the effect of the same intervention on the same outcome are identified, and data are sufficiently available, these data are pooled. If between-study variation is anticipated, the reviewers will perform random effects meta-analyses using the Review Manager 5 software. The Mantel-Haenszel method and the Inverse-Variance method are used for dichotomous and continuous outcomes, respectively. Meta-analysis results are visually presented in forest plots.

If the number of interventions is sufficiently high, the heterogeneity in reported outcomes is manageable, and enough data are available, network meta-analyses may be performed as well.[7]

In case a quantitative synthesis is not possible, study findings are synthesised narratively, taking into account the overall certainty of the body of evidence. Forest plots may be used to visualize the results of the individual studies.

Subgroup analysis and investigation of heterogeneity

To investigate potential heterogeneity, the CEBaP reviewers may conduct a number of a priori determined subgroup analyses. Should post hoc subgroup analyses be conducted, the reviewers clearly state in the review that these analyses are post hoc and exploratory in nature.

As direct analysis of more than two subgroups is not possible in the Review Manager 5 software, subgroups are compared two by two, whether the outcome is continuous or dichotomous. P-values are appropriately adjusted for multiple testing.

Sensitivity analysis

Sensitivity analyses may be performed to test the robustness of the meta-analysis results by assessing the impact of notable assumptions, imputed data, borderline decisions and studies at high risk of bias.

'Summary of findings' table

In the context of a Cochrane systematic review, a 'Summary of findings' table is created for the most relevant comparison of interventions using the GRADEpro software.[8] Additional tables may be created for other relevant comparisons as well.

The table contains information on the extracted data (i.e. the effect measures, confidence intervals and p-values) for all primary and secondary outcomes of the review. In addition, it contains information on the certainty of the body of evidence for each outcome, which is evaluated using the GRADE approach.

3. Where can I find the systematic reviews conducted by CEBaP?

All of our systematic review publications are bundled in the Publications section of our website.

In order to guarantee the quality of our systematic reviews, CEBaP makes sure to:

- Call on the expertise of at least 1 external content expert, before submitting the review manuscript for publication in a peer-reviewed journal. (S)he is asked to provide an independent appraisal of the quality and relevance of particular aspects of the review, which helps to improve the quality even further;
- Adhere to the 27-item PRISMA checklist and the 12-item PRISMA extension for Abstracts for clear and transparent reporting in a publication.

PART 2: PROJECT INITIATION AND FLOW

A) PROJECT INITIATION

A graphical representation of the **project initiation and project flow** can be found in **Appendix 2**.

1. Project application

Before CEBaP can start with the development of an evidence-based practice guideline or systematic review, a project application should be filled in and submitted by the requesting Belgian Red Cross service or external party.

2. CEBaP Steering Committee decision: guideline, systematic review or no project

The filled in project application is reviewed by the CEBaP Steering Committee, which is composed of:

- The manager of CEBaP;
- The coordinating researcher of CEBaP;
- The Director of Humanitarian Services of the Belgian Red Cross;
- The Medical Director of the Blood Service of the Belgian Red Cross;
- The manager of the International Cooperation of the Belgian Red Cross;
- The Director of the Marketing and Communications department of the Belgian Red Cross;
- The CEO of the Belgian Red Cross.

The Committee decides if:

1) A practice guideline project will be initiated;
2) A systematic review will be developed;
3) No new project will be started up.

A guideline project will be initiated if:

- the guideline may have a high impact on practice or on society;
- there is a high sense of urgency;
- there is a chance that it will result in a peer-reviewed publication;
- the project may have an economic and financial impact on the Belgian Red Cross;
- the project fits into the research strategy of the Belgian Red Cross.

If the number of suitable topics within an evidence-based guideline exceeds the feasible amount of topics, the same criteria are used to prioritize the different (sub)topics.

During the development of an evidence-based practice guideline, it often becomes clear where an up-to-date overview on the effectiveness of interventions is lacking. In these cases, the CEBaP Steering Committee can decide to develop a systematic review. In other words, once completed, every systematic review performed by CEBaP serves as evidence that supports future guideline development.

A systematic review will only be developed if:

- the review can be used to advocate policy change;
- there is a low sense of urgency;
- there is a major chance that it will result in a peer-reviewed publication;
- the quality of the body of evidence is moderate to high (preferably).

B) PROJECT FLOW

Once the Steering Committee has reached its decision, the responsibility of the literature search is assigned to one or more CEBaP researchers. The systematic literature searches are conducted according to the methodological standards described in Part 1 of this charter, in close collaboration with the requesting party.

REFERENCES

1) Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, Fervers B, Graham ID, Grimshaw J, Hanna SE, Littlejohns P, Makarski J, Zitzelsberger L; AGREE Next Steps Consortium. *AGREE II: advancing guideline development, reporting and evaluation in health care.* CMAJ 2010, 182(18):E839-42. doi: 10.1503/cmaj.090449.

2) Scottish Intercollegiate Guidelines Network (SIGN). *SIGN 50: a guideline developer's handbook*. Edinburgh: SIGN; 2015. (SIGN publication no. 50). [November 2015]. Available from http://www.sign.ac.uk

3) Schünemann H, Brozek J, Guyatt G, & Oxman A (eds.) (2013). *GRADE Handbook – Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach [updated October 2013].* GRADE Working Group, 2013. Available from https://gdt.gradepro.org/app/handbook/handbook.html

4) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer T, Varonen H, Vist GE, Williams JW Jr, Zaza S; GRADE Working Group. *Grading quality of evidence and strength of recommendations.* BMJ 2004, 328(7454):1490.

5) Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

6) Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JPT. *ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions*. BMJ 2016; 355; i4919; doi: 10.1136/bmj.i4919.

7) Chaimani A, Caldwell DM, Li T, Higgins JPT, Salanti G. *Chapter 11: Undertaking network meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions.* London: Cochrane.

8) GRADEpro GDT: *GRADEpro Guideline Development Tool [Software]*. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org.

9) Peters MDJ, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, McInerney P, Godfrey CM, Khalil H. *Updated methodological guidance for the conduct of scoping reviews*. JBI Evid Implement. 2021 Mar;19(1):3-10. doi: 10.1097/XEB.0000000000000277. PMID: 33570328.

10) Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, Moher D, Peters MDJ, Horsley T, Weeks L, Hempel S, Akl EA, Chang C, McGowan J, Stewart L, Hartling L, Aldcroft A, Wilson MG, Garritty C, Lewin S, Godfrey CM, Macdonald MT, Langlois EV, Soares-Weiser K, Moriarty J, Clifford T, Tunçalp Ö, Straus SE. *PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation*. Ann Intern Med. 2018 Oct 2;169(7):467-473. doi: 10.7326/M18-0850. Epub 2018 Sep 4. PMID: 30178033.

ABBREVIATIONS AND GLOSSARY

AGREE II

*Short for **A**ppraisal of **G**uidelines for **Re**search & **E**valuation **II***

The AGREE II instrument is a 23-item tool that was developed to enable the assessment of the methodological rigour and transparency used during guideline development.

Bias

In case of bias, a systematic error is introduced into a study. As a result, the magnitude or direction of study results may differ from reality. Bias can enter scientific studies at all stages: during study preparation, data collection, data analysis and interpretation, as well as during the reporting phase. An overview of biases which may distort the design, execution, analysis and interpretation of research in healthcare, is listed in the Catalogue of Bias.

Cochrane

A global independent network that promotes evidence-informed health decision-making by producing high-quality, relevant, accessible systematic reviews and other synthesized research evidence. Cochrane is internationally recognized as the benchmark for high-quality information about the effectiveness of health care.

GRADE

*Short for **G**rading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuation*

A systematic approach to rating the certainty of the best available evidence in evidence syntheses (e.g. systematic reviews, guidelines, health technology assessments) and grading the strength of guideline recommendations. GRADE offers a transparent and structured process for developing and presenting evidence summaries and for carrying out the steps involved in developing recommendations.

Grey literature

Information produced by governments, academics, business and industry, that has remained unpublished or has not been published commercially. Common grey literature publications are government reports, policy statements, preprint materials, technical reports, conference proceedings, ongoing clinical trials, theses and dissertations.

PICO question

*Short for **P**opulation, **I**ntervention, **C**omparison and **O**utcome question.*

A research question that precisely defines the population, intervention, comparison and outcome of interest.

APPENDIX 1: EVIDENCE SUMMARY TEMPLATE

Topic	
Subtopic	
Intervention	
Question (PICO)	
Search Strategy	
Search date	
In/Exclusion criteria	

Characteristics of included studies

Author, year Country	Study design	Population	Comparison/Risk factor/Exposure	Remarks

Synthesis of findings

Outcome	Comparison/Risk factor/Exposure	Effect Size	#studies, # participants	Reference

Study limitations

Version 1: Experimental studies

Author, Year	Lack of allocation concealment	Lack of blinding	Incomplete accounting of outcome events	Selective outcome reporting	Other limitations

Version 2: Observational studies

Author, Year	Inappropriate eligibility criteria	Inappropriate methods for exposure and outcome variables	Not controlled for confounding	Incomplete or inadequate follow-up	Other limitations

Version 3: Diagnostics

Author, Year	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?	Other limitations

Certainty of the body of evidence

	Initial grading, e.g. High [A]	Downgrading due to
Limitations of study design	0	See table 'Study limitations'
Imprecision	0	[Limited sample sizes/low number of events/lack of data/large variability of results]
Inconsistency	0	
Indirectness	0	
Publication bias	0	
		Upgrading due to
Large magnitude of effect	0	
Dose-response gradient	0	
Plausible confounding	0	
QUALITY (GRADE)	**Final grading, e.g. Low [C]**	

Conclusion	
Update status	
Reference(s)	

APPENDIX 2: PROJECT INITIATION AND PROJECT FLOW