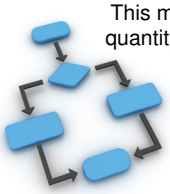

Systematic Reviews

Kerry A. Milner, DNSc, RN

Systematic reviews are a type of literature review in which authors systematically search for, critically appraise, and synthesize evidence from several studies on the same topic (Grant & Booth, 2009). The precise and systematic method differentiates systematic reviews from traditional reviews (Khan, Kunz, Kleijnen, & Antes, 2003). In all types of systematic reviews, a quality assessment is done of the individual studies that meet inclusion criteria. These individual assessments are synthesized, and aggregated results are reported. Systematic reviews are considered the highest level of evidence in evidence-based health care because the reviewers strive to use transparent, rigorous methods that minimize bias.

High-quality systematic reviews are precise, detailed critical summaries of all available primary research on a topic and should be used by nurses to answer clinical questions. Nurses also should incorporate this type of evidence when making practice improvements or developing guidelines. In addition, researchers in nursing looking for funding likely will conduct a systematic review or use an existing review to establish the state of the science in an area. This process of using existing systematic reviews or conducting new ones will help to advance the science of nursing.

The number of published systematic reviews has exploded since the inception of the Cochrane Collaboration 20 years ago. In 1995, the Cochrane Database of Systematic Reviews (CDSR) included 36 reviews, and in 2012, the CDSR included more than 5,200 (MacLehose & Hilton, 2013). During this time, the process for preparing and reporting systematic reviews has undergone changes. Transparency for all aspects of the review process has been encouraged because published reviews that are well done and minimize bias are very important if the results will be used to make practice decisions (Tunis, McInnes, Hanna, & Esmail, 2013). Standards for reviews that have been adopted by the Cochrane Collaboration, Campbell Collaboration, and Joanna Briggs Institute (JBI) are comprised of reviews that include research groups with specialized skills; international evidence that is translated into easy-to-understand brief reports that can be adapted to practice settings around the world; and rigorous and explicit methods to ensure that the results are reliable and meaningful. The purpose of this article is to present an overview of the types of systematic reviews, where to find systematic reviews, the systematic review process, critical appraisal of systematic reviews, and resources for systematic review training.

Types of Systematic Reviews

Types of systematic reviews are defined by the level of evidence that is most appropriate for answering the review question as well as the research designs of the studies selected for inclusion in the review. A quantitative systematic review may include randomized, controlled trials (RCTs) only, a mix of experimental and quasi-experimental study designs, or observational studies only. Qualitative systematic reviews include studies that use qualitative research designs. The Cochrane Collaboration, which solely had supported and published quantitative reviews, published its first qualitative systematic review in November 2013. The reason for this is that most effectiveness or treatment- and therapy-related clinical questions are best answered with the least amount of bias, using quantitative research designs, whereas questions about values or beliefs are best answered with qualitative systematic reviews.

The type of studies that are included in a review is driven mainly by the available literature that is relevant to the review question. Systematic reviews cannot be done if no literature exists to review, nor is doing a review worthwhile if the level of evidence of the available studies is not sufficient for the type of clinical question. DiCenso, Guyatt, and Ciliska (2005) identified specific types of systematic reviews that are best for answering four types of clinical questions.

- Meta-analysis or systematic review of RCTs for treatment comparison
- Systematic review of cohort, case-control studies for determining the extent of risk and prediction of future problems
- Systematic review of blinded comparison test and reference value for evaluating specificity or sensitivity of an assessment or test
- Meta-synthesis of qualitative studies for examining perceptions, values, or beliefs.

Finding Systematic Reviews

Several international collaborations have the common goal of providing reliable, up-to-date evidence about effective interventions that can be used by clinicians, administrators, policymakers, researchers, and the public to make decisions about health or social care. Systematic reviews can be found by searching registries of organizations (see Figure 1).

Each registry has different guidelines for registering, conducting, and reporting a systematic review. The Cochrane

ONF, 42(1), 89–93.
doi: 10.1188/15.ONF.89-93

The Campbell Collaboration Library
www.campbellcollaboration.org/lib

The Cochrane Collaboration Cochrane Reviews
www.cochrane.org/cochrane-reviews

The Joanna Briggs Institute
www.joannabriggs.org/research/registered_titles.aspx

York Centre for Reviews and Disseminations (PROSPERO)
www.crd.york.ac.uk/PROSPERO

Figure 1. Organizations With Systematic Review Registries

Collaboration, Campbell Collaboration, and JBI have a process by which the systematic review protocols are peer reviewed and approved before the authors can register. In contrast, York Centre for Reviews and Disseminations (PROSPERO) checks the protocol against its criteria and the review must reflect the effects of interventions and strategies to prevent, diagnose, treat, and monitor health conditions for which a health outcome exists. The Campbell Collaboration and JBI require exhaustive systematic searches that include unpublished reports to avoid publication bias. Except for PROSPERO, verification of systematic review training and active involvement in systematic review development is preferred to register a review. Registries of systematic reviews are helpful because they can reduce unplanned duplication of reviews on the same topic, promote high-quality standards, and support the transparency of the review process (Straus & Moher, 2010).

Conducting a Systematic Review

All systematic reviews have several common features, regardless of the type of evidence used in the review. These include developing a review question and protocol, searching for evidence, selecting studies, performing quality appraisal of individual studies, extracting data, pooling the data and data synthesis, and reporting results. The Cochrane Collaboration provides a free handbook for systematic reviews that details the process of conducting a review and can be downloaded from www.handbook.cochrane.org (Higgins & Green, 2011). The following is an overview of the steps for conducting a systematic review.

Assemble a team: Systematic reviews must be conducted by a group of researchers, because more than one reviewer is needed to complete the review at different points in the process. When assembling a team for the review, including people who have expertise in the content under study, systematic review methods, statistics and meta-analyses, and reference management is advisable. Including a health sciences librarian who will help with identifying appropriate databases and other sources for evidence and the search is also recommended.

Develop a review question: The patient problem or population, intervention, comparison, and outcome (PICO) method is often used for developing a systematic review question. This method helps the reviewers formulate a specific and explicit question that will make searching for relevant studies easier.

Develop the protocol for study inclusion: The protocol should have clearly stated criteria for how studies will be selected for inclusion in the review. The types of participants, interventions or phenomena of interest, outcomes, and studies must be specified in detail in the protocol. The protocol should go through a peer review process. For reviews sponsored by the Cochrane Collaboration, Campbell Collaboration, and JBI, authors must submit their protocol to the organization's peer review process and obtain approval before proceeding to the next step of searching for studies. Step two is very important because it drives the rest of the process and the studies that are included in the review and, ultimately, the results of the review.

Search for studies: The search strategy should be explicit so that another research group can replicate the search and obtain the same studies. Exhaustive searching should be done in all the appropriate databases. Some popular databases for healthcare literature include PubMed, MEDLINE®, CINAHL®, EMBASE, PsycINFO, and CDSR. Because searches for evidence must be exhaustive to minimize publication bias, some organizations, like the Campbell Collaboration and JBI, require research groups to search unpublished evidence such as dissertations, conference proceedings or abstracts, and summaries posted on government or practice websites. Other potential biases that may occur during searching are database and language bias. If the reviewers limit their search to MEDLINE, CINAHL, and CDSR, potential studies in journals that are not indexed in these databases would be missed. Using only studies written in English also may bias the search. Reviewers should keep track of and report non-English studies that meet the inclusion criteria and, if possible, have a member of the review group who is fluent in that language appraise the study. Research groups commonly partner with a health sciences librarian who has knowledge and expertise in searching and finding relevant evidence, which helps limit potential bias.

Reviews with a healthcare focus may follow a three-step search strategy in which the initial search is done in MEDLINE and CINAHL databases looking for all relevant controlled terms (Medical Subject Headings [MeSH]) and keywords in the title or abstract. A second search is done with all the controlled terms and keywords found in the initial search. A third search, also called a hand search, involves the reviewers searching the reference lists of all relevant articles.

Select studies for retrieval: Selecting studies for retrieval requires strict adherence to the review protocol that details the criteria for considering studies for inclusion based on types of participants, interventions, outcome measures, and study designs. In this step, reviewers merge the searches from the different databases and remove any duplicate studies. Reviewers then read the titles and abstracts and remove any irrelevant studies and obtain the full text of the keeper studies. Reviewers evaluate the keeper studies against the study inclusion criteria. Other members of the research group check study eligibility for any studies that were questionable. Two or more members in the group make the final decision on what studies to include in the review. Some reviewers may calculate and report a kappa statistic for this process, which is a measure of agreement. This whole process should be described in detail in the methods section of any published systematic review so readers can assess the decision-making process behind how the studies were selected for inclusion.

Data extraction: To provide a measure of quality, data extraction from the selected studies should be conducted using a data extraction tool; be completed by at least two group members with previous data extraction training;

and include two data extractors for each study who separately extract data (blind extraction) before comparing results. The JBI has software for this purpose that can be accessed by members. The Cochrane Collaboration has a free data extraction tool that can be downloaded from its website (www.cochrane.org). Regardless of the tool used, the purpose of this step is to create an organized and systematic process for extracting data that are pertinent to the review question and include information on the method, setting, number of participants and their baseline characteristics, interventions, outcomes, and results that will be analyzed and synthesized in later steps.

Data extraction can be challenging and time consuming because reviewers are working toward pooling the data of many studies that often are heterogeneous. While extracting data, reviewers need to consider how the data fit with the review question and evaluate if the individual studies are comparable. Reviewers are looking for similarity in populations, outcome measures, instruments and scales used for measuring outcomes, and delivery of interventions. Data are extracted from each study by at least two reviewers, and the extracted data are checked for differences. If discrepancies persist, another reviewer may be needed to reconcile the differences.

Quality assessment and critical appraisal of the individual studies: Assessing the quality of the individual studies is important because combining the results of poor-quality research may lead to inaccurate, biased conclusions. In this step, the validity and potential sources for bias are established. For each study, reviewers are making judgments about whether the quality issues are minor or major. Major quality issues are study flaws that decrease the reviewer's confidence in the results.

In quantitative systematic reviews using experimental or quasi-experimental studies, the major biases that are assessed in the individual studies include selection, performance, detection, and attrition. Selection bias is defined as preexisting differences between groups at baseline, and randomization is the best strategy for minimizing this bias. Allocation concealment also is helpful in reducing this bias by making sure that participants are unaware of their group assignment at the time of enrollment. Performance bias refers to systematic differences in delivery of care other than the intervention. It is best mitigated by blinding or masking the intervention, or concealing the intervention group from the investigators and participants. Detection bias occurs when systematic differences exist in how the outcomes are measured in each group. This type of bias may be addressed by blinding the people responsible for collecting data on the outcome measures. Attrition bias refers to systematic differences in withdrawals or exclusions between study groups. This potential bias can be addressed by detailed reporting of losses and withdrawals, and use of the intention-to-treat analysis. Intention-to-treat is an analysis that is conducted in RCTs only and in which participants are analyzed in the group they originally were assigned.

Critically appraising the individual studies for reviews that include observational studies can be more challenging because the designs (e.g., cohort, case control, cross-sectional) do not share common methodologic features like RCTs (e.g., randomization, allocation concealment, blinding). In systematic reviews using observational studies, the major biases that are assessed in the individual studies include sample, selection, loss to follow-up, and detection. Sample bias occurs when the sample is not representative of the target population. Reviewers make a judgment about sample bias, and if it is determined to be significant, the study will be excluded. Because sample bias is always a concern with systematic reviews that use studies with observational designs, the reviewers should be cautious about the reported results and include the characteristics of the group they represent. Selection bias is a potential threat because participants are not randomized and may have baseline differences that may confound the true cause of the observed outcome. Reviewers should evaluate the individual studies included in the review and assess baseline characteristics to establish that the study groups were comparable. Loss to follow-up bias refers to different dropout rates between study groups (e.g., deaths from exposure to outcome of interest), or when the participants who withdraw from the study are different from those who complete the study (e.g., participants who drop out may be more likely to have the outcome of interest). Reviewers should determine whether to include the study based on the amount of loss, with less than 5% loss leading to a little bias and more than 20% posing a serious threat to study validity (Dettori, 2011). Detection bias is also a potential threat in observational studies. Nothing can be done to address this bias other than being aware that it is a potential bias, and, if considered a serious threat to validity, the study should be excluded from the review.

The goal of critical appraisal is to reject poor-quality studies and keep the high-quality studies for the review. Appraisal tools for assessing the quality or risk for bias in individual studies are available.

Critical appraisal of each study must be done by at least two reviewers. After appraising each study with an agreed-on tool, the reviewers compare results and discuss any discrepancies. The final decision to keep or discard the study should be based on a prespecified definition of high-quality study versus low-quality study, and the cutoff point between these endpoints that is acceptable to the review team.

Data synthesis and meta-analysis: Data synthesis varies depending on the type of review question. All reviews should address contradictory findings, limitations because of study methods, quality issues, and future research. If the review is on the effectiveness of an intervention, data synthesis also should include the intervention effect and effect size; if the intervention effect was clinically meaningful; if the effect was consistent across studies; and if factors impacted the likelihood of seeing the effect.

Meta-analysis is the process by which data are extracted from more than one study and statistical analyses are performed. Meta-analysis may not be possible for all of the studies in a review because data may not be reported, or too much heterogeneity exists among studies. Therefore, meta-analyses may be conducted on a subgroup of studies within a systematic review. Because these analyses can be quite complex and require many decisions, an expert in meta-analyses is advantageous in assisting with this part of the review.

Present results, summary of findings, and conclusions: In this step, reviewers usually present the descriptive findings from each study in a table format with columns for the population being studied, the interventions (with effects), outcomes, and any methodologic

issues or biases. Reporting this information is important so readers can appraise the appropriateness and quality of the studies included in the review, as well as the applicability to local practice. Readers also can use data from this table to assess the appropriateness of pooling the data for meta-analysis.

Conclusions and recommendations are based on the quality of the studies included in the review and the confidence in the results when pooling data. If the review includes moderate- to low-quality studies, the ability to make strong recommendations is limited. If the review includes several high-quality studies that pooled the data and found that the magnitude of the effect of the intervention was stronger, then strong recommendations can be made. Having an abundance of studies on a topic that are of low quality is possible, and putting them together in a systematic review does not elevate their quality. In this instance, the systematic review can be helpful in providing direction for future research.

Dissemination: Similar to manuscripts of individual studies, systematic reviews can be disseminated in the traditional manner of publication in appropriate journals. This type of dissemination can slow the translation of evidence into practice because healthcare providers may lack the time, skills, and resources for retrieving, appraising, and integrating knowledge from published systematic reviews (Oermann, Floyd, Galvin, & Roop, 2006). A strategy to overcome these barriers is providing easy-to-understand brief reports of systematic reviews that can be targeted to appropriate audiences and sent by email. However, what dissemination strategies are most effective is not clear. In a systematic review on strategies to communicate and disseminate evidence, reviewers concluded that multicomponent strategies that include reach of information (e.g., postal service, email, social and mass media), include motivation to use and apply evidence (e.g., use of champions, peer and social networks), and provide "how to" information to bridge adoption to implementation appear to be more effective than one strategy alone (McCormack et al., 2013). Additional studies on effective strategies for knowledge transfer to clinical practice need to be conducted.

The time required to do a review also impacts dissemination of timely evidence. Although systematic reviews are considered the gold standard for knowledge synthesis, completing a high-quality review can take too long. Reviews can take from six months to two years to complete and attempt to answer a narrow clinical question (Khangura, Konnyu, Cushman, Grimshaw, & Moher, 2012). Additional studies need to be directed at how to accelerate the process and still maintain quality.

Critical Appraisal of Systematic Reviews

Several tools are available for assessing the methodologic quality and rigor of systematic reviews. The Critical Appraisal Skills Programme (CASP) tool for critical appraisal of systematic reviews is free to download from the CASP International Network website at www.casp-uk.net. Although the original intent of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was to improve the reporting of systematic reviews and meta-analyses in the literature, this checklist can be downloaded for free at www.prisma-statement.org, and the questions can be used as a guide for assessing the quality of the review. Both tools help users assess the validity of the results and relevance of the results to practice.

Training for Conducting Systematic Reviews

To improve the number of high-quality reviews on which practice decisions can be made, reviewers having systematic review training before starting a review is vitally important. Several free and fee-based systematic review training resources in the United States and abroad are offered online or in person. The Campbell Collaboration Resource Center has a series of free online training videos that provide an introduction to systematic reviews and their basic elements. Cochrane has the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins & Green, 2011). It also has free online interactive learning opportunities on systematic reviews. JBI offers in-person short courses on systematic reviews for a fee in the United States and abroad (www.joannabriggs.org/jbi-education.html). The Agency for Healthcare Research and Quality has free online training modules that detail all the steps of the systematic review process (www.ahrq.gov).

Conclusion

A high-quality systematic review requires considerable planning and resources. Serious thought goes into developing a clear and explicit review question and protocol. Large amounts of time and effort are spent on searching the literature, selecting and critically appraising the studies, and synthesizing data into meaningful, useful conclusions. At several points in the review process, if reviewers are not adequately trained, negative consequences can occur. If the review question and protocol are not explicit and clear, the search for appropriate studies becomes haphazard. If the literature search is not exhaustive, important studies or evidence may be missed. Reviews that have low-level evidence, have a mismatch between level of evidence and question type, or include studies that lack methodologic rigor are not very useful to healthcare providers or nurses in the clinical setting.

Despite those issues, systematic reviews have the potential to substantially improve health care and nursing science. Nurses routinely should assess and incorporate evidence from systematic reviews into their practice. Researchers in nursing should conduct systematic reviews on relevant topics and disseminate findings to drive practice change. An area that needs additional studies is how to do a quality review faster and get it into the hands of nurses and other healthcare providers in such a form that is easily implemented into practice.

Kerry A. Milner, DNSc, RN, is an assistant professor at Sacred Heart University in Fairfield, CT. No financial relationships to disclose. Milner can be reached at milnerk@sacredheart.edu, with copy to editor at ONFEditor@ons.org.

References

Dettori, J.R. (2011). Loss to follow-up. *Evidence-Based Spine-Care Journal*, 2, 7–10. doi:10.1055/s-0030-1267080

DiCenso, A., Guyatt, G.H., & Ciliska, D. (2005). *Evidence based nursing: A guide to clinical practice*. St. Louis, MO: Elsevier Mosby.

Grant, M.J., & Booth, A. (2009). A typology of reviews: An analysis of 14 review types

and associated methodologies. *Health Information and Libraries Journal, 26*, 91–108. doi:10.1111/j.1471-1842.2009.00848.x

Higgins, J., & Green, S. (2011). *Cochrane handbook for systematic reviews of interventions* (version 5.1.0). Retrieved from http://handbook.cochrane.org

Khan, K.S., Kunz, R., Kleijnen, J., & Antes, G. (2003). Five steps to conducting a systematic review. *Journal of the Royal Society of Medicine, 96*, 118–121. doi:10.1258/jrsm.96.3.118

Khangura, S., Konnyu, K., Cushman, R., Grimshaw, J., & Moher, D. (2012). Evidence summaries: The evolution of a rapid review approach. *Systematic Reviews, 1*, 10. doi:10.1186/2046-4053-1-10

MacLehose, H., & Hilton, J. (2013). Changes to the Cochrane Library during the Cochrane Collaboration's first 20 years. Retrieved from http://thecochranelibrary.com/details/editorial/4282481/Changes-to-The-Cochrane-Library-during-The-Cochrane-Collaborations-first-20-year.html

McCormack, L., Sheridan, S., Lewis, M., Boudewyns, V., Melvin, C.L., Kistler, C., . . . Lohr, K.N. (2013). Communication and dissemination strategies to facilitate the use of health-related evidence. Retrieved from http://ncbi.nlm.nih.gov/books/NBK179104

Oermann, M.H., Floyd, J.A., Galvin, E.A., & Roop, J.C. (2006). Brief reports for disseminating systematic reviews to nurses. *Clinical Nurse Specialist, 20*, 233–238. doi:10.1097/00002800-200609000-00009

Straus, S., & Moher, D. (2010). Registering systematic reviews. *Canadian Medical Association Journal, 182*, 13–14. doi:10.1503/cmaj.081849

Tunis, A.S., McInnes, M.D., Hanna, R., & Esmail, K. (2013). Association of study quality with completeness of reporting: Have completeness of reporting and quality of systematic reviews and meta-analyses in major radiology journals changed since publication of the PRISMA statement? *Radiology, 269*, 413–426. doi:10.1148/radiol.13130273