Systematic Reviews and Meta-Analysis

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Background: Systematic reviews and meta-analyses are important research tools in modern medicine. They serve to condense and clarify large amounts of data into resources that can educate clinicians, enhance patient care, help formulate clinical guidelines, and guide future research endeavors.
Methods: The existing literature, including recently updated guidelines, on systematic reviews and meta-analysis was reviewed and summarized.
Results: A brief background on the origins of systematic reviews is presented, and the advantages and disadvantages of this type of study are discussed. A step-by-step guide to conducting a proper systematic review is outlined, with many illustrative examples. The recently updated reporting guidelines for this type of study are included.
Conclusions: Using clinical examples and published guidelines, a framework is presented to help the reader properly conduct a systematic review. These guidelines also help the reader conduct a critical appraisal of systematic reviews published in the scientific literature. Even more importantly, principles regarding application of systematic review results to individual patients are addressed. (*Plast. Reconstr. Surg.* 127: 955, 2011.)

Evidence-based medicine is most commonly defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[1] Systematic reviews are an important component of evidence-based medicine, inasmuch as they summarize existing knowledge and data on a particular topic, providing us with the "best evidence" needed to make clinical decisions.

Since this topic was last reviewed in this journal,[2] updated reporting guidelines have been developed regarding the reporting of systematic reviews and meta-analyses.[3] This article will first provide some background information regarding these types of studies, including inherent advantages and disadvantages. Next, a step-by-step guide to conducting a systematic review will be presented, along with clinical examples to illustrate each step. The reporting guidelines [Meta-analysis of Observational Studies in Epidemiology (MOOSE)[4] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[3]] will be reviewed and discussed; these "checklists" identify the items that should be included in every systematic review. As such, they can be helpful in preparation of your own review or in critical appraisal of reviews published in the scientific literature. Finally, issues regarding generalizability of findings to individual practices and patients will be discussed.

WHAT IS A SYSTEMATIC REVIEW?

As the body of medical literature continues to expand, reviews have become essential tools to summarize existing knowledge. Traditional narrative reviews often fail to use scientific methods and are therefore subject to significant bias.[5] In an effort to reduce this bias and improve the scientific rigor of reviews, the systematic review was developed in the 1990s. Chalmers and Altman[6] defined the systematic review as "a review that has been prepared using a systematic approach to minimizing biases and random errors which is documented in a materials and methods section." The *Cochrane Handbook*'s definition of a systematic review is one that "attempts to collate all empirical evidence that fits prespecified eligibility criteria to answer a specific research question. It uses ex-

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plicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made."[7]

As might be inferred by the above definitions, systematic reviews are conducted according to structured guidelines to maintain their scientific integrity and minimize bias. The earliest of these guidelines drew on the social science and psychology literature.[8] Modern guidelines for systematic reviews have been developed by international groups of experts that have included review authors, methodologists, clinicians, medical editors, and consumers. These guidelines are typically referred to by a convenient acronym, examples of which are QUOROM, Quality of Reporting of Meta-Analyses; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; and MOOSE, Meta-analysis of Observational Studies in Epidemiology.[3,4,9] These will be discussed in more detail later in this article.

Systematic reviews may or may not include a meta-analysis. Meta-analysis is defined as the use of statistical methods to summarize the results of independent studies.[10] Meta-analysis studies are technically a subset of systematic reviews: every meta-analysis requires a systematic review of the literature, but not every systematic review yields data suitable for pooling in a meta-analysis.[11]

As a research tool, systematic reviews are helpful in several situations (Table 1). When a particular field of study, such as "limb salvage," involves such a large accumulation of original research (Fig. 1) that reviewing every article on the topic is enormously challenging, systematic reviews can objectively synthesize the data into summary form.[12] If original studies, editorials, and narrative reviews on a topic offer conflicting opinions or results, a systematic review can often help resolve this uncertainty. In select cases, pooling of data via meta-analysis can help studies with small numbers of subjects attain statistical significance that was not possible on their own. Finally, systematic reviews can help identify areas where the current body of evidence is insufficient and additional studies are required.[11]

Table 1. Applications of Systematic Reviews and Meta-Analysis

Systematic reviews can:
Summarize large numbers of original studies
Resolve uncertainty when original studies disagree
Help smaller studies reach statistical significance (meta-analysis)
Identify areas for future research

ADVANTAGES, DISADVANTAGES, AND BIAS

As a research design, the systematic review offers many inherent advantages. As discussed above, this type of analysis can reduce the bias and random error found in many narrative reviews and can help synthesize data from smaller studies to reach statistical significance. Furthermore, because the methods for conducting a systematic review are both transparent and reproducible, any given study can be easily updated as new data are published.[13,14]

Systematic reviews are highly ranked among the levels of evidence for published studies (Table 2)[15,16] and are also cited with greater frequency than other types of studies. In fact, when evaluating studies of treatment effects, meta-analyses were found to be cited even more than randomized controlled trials.[17]

The disadvantages of systematic reviews are related to sources of bias—primarily publication bias, citation bias, and language bias. Although biases can be minimized with careful study design, there are certain types of bias that are inherently problematic when performing a systematic review. The most important bias to consider is publication bias.[18] This refers to the selective publication of studies with positive or statistically significant results.[19] For instance, it has been shown that studies with positive results are three to eight times more likely to be published.[20] Furthermore, studies with positive results are more likely to be published in journals with higher citation indexes, and they are more likely to generate multiple publications than negative studies. The obvious concern is that well-designed studies—even randomized controlled trials—that do not have statistically significant results may not be published, and a review of the published literature will therefore overestimate the positive effect of a particular intervention.

Many solutions to publication bias have been proposed. First, a comprehensive search of unpublished studies should be included whenever a systematic review is conducted. This includes researching conference proceedings, correspondence with experts in the field, and review of the appropriate clinical trial registries. Both the National Institutes of Health[21] and the Cochrane Collaboration[22] maintain clinical trial registries. Many journals now require that clinical trials be prospectively registered before the enrollment of patients.[23] It is only with prospective registration of

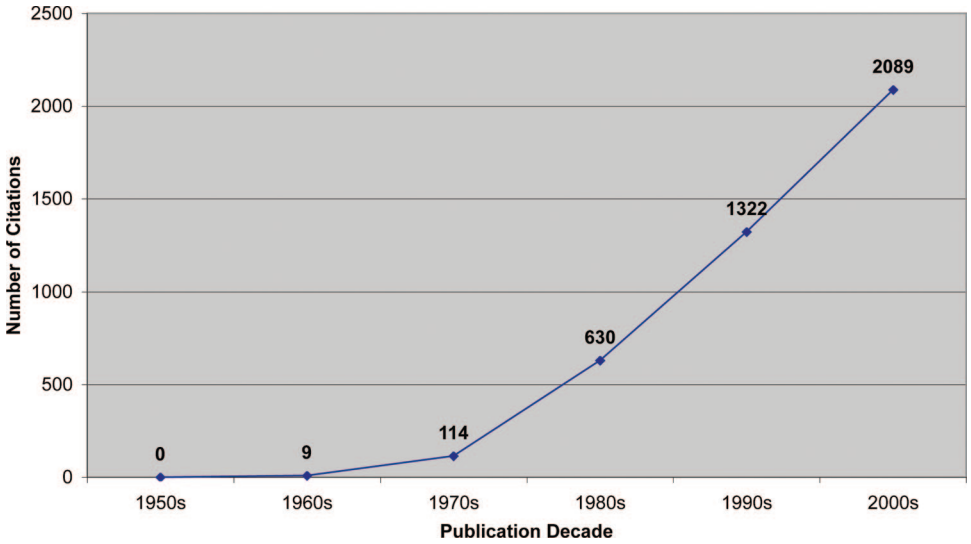

Fig. 1. MEDLINE citations for "limb salvage" by decade.

Table 2. University of Oxford Centre for Evidence-Based Medicine's Levels of Evidence (Highest to Lowest)*

Level of Evidence	Study Design
1a	Systematic review of randomized controlled trials
1b	Individual randomized controlled trial
1c	"All or none" case series
2a	Systematic review of cohort studies
2b	Individual cohort study or low-quality randomized controlled trial
2c	Ecological study
3a	Systematic review of case-control studies
3b	Individual case-control study
4	Case series or poor-quality cohort or case-control study
5	Expert opinion

*Oxford Centre for Evidence-Based Medicine: Levels of Evidence (March 2009). Available at: http://www.cebm.net/index.aspx?o=1025. Accessed January 8, 2010.

all clinical trials that we can truly capture all existing data and completely eliminate publication bias.

Citation bias is closely related to publication bias. This phenomenon occurs when the chance of a study being cited by others is associated with its results. This has worked both ways: some studies have found that positive studies are cited more by others,[24] whereas other studies have showed the opposite.[25]

Another important source of bias is language bias. This form of bias occurs when the language(s) of publication depend on the study's results.[18] For example, it has been shown that authors were more likely to publish randomized controlled trials in an English-language journal, as opposed to a German-language journal, if the results were statistically significant.[26] If a systematic review were then conducted that excluded non-English journals, the conclusion of the review would be unfairly biased toward a statistically significant result. This is a significant source of bias, as non-English publications are excluded in the majority of meta-analyses published in English-language journals.[27] To eliminate language bias, the review must make significant efforts to obtain non-English language references and have them appropriately translated to include the data in the review.

Systematic reviews may be designed to include only randomized controlled trials,[9] or they can be constructed to include observational studies, such as prospective cohort studies, case-control studies, cross-sectional studies, or case series.[4] In fact, systematic reviews of reviews have been published.[28,29] The ultimate level of evidence achieved by a systematic review depends on the quality of the studies that are included in the review (Table 2). Systematic reviews based on observational studies are subject to additional bias due to the nonrandomization of study subjects. Because of this, patient selection bias and treatment allocation bias present in the original observational studies can affect the outcome of the systematic review of those studies.

One last word of caution applies to meta-analysis. As indicated above, meta-analysis is essentially a statistical manipulation of data pooled from other studies. Data from individual studies should only be pooled for meta-analysis if the studies are both independent and similar. Increased heterogeneity between the individual studies will lead to

inaccuracy of the meta-analysis. Because of the additional complexity involved in adding meta-analysis to a systematic review, it is strongly recommended that a statistician or epidemiologist be included in the planning and execution of this type of study.

CONDUCTING A SYSTEMATIC REVIEW

The proper steps for conducting a systematic review are outlined in Table 3. Although each of these will be discussed in this article, those wishing to learn more are referred to the original text by Egger and Smith, from which this list was extracted.[30] It is helpful to think of a systematic review as an observational study of the available evidence. As with any research study, the protocol should be written in advance to avoid introducing bias along the way. For example, if studies are uncovered with unexpected results, one must avoid *post hoc* modification of the inclusion or exclusion criteria to exclude that particular study. Typically, the a priori determined review protocol should include steps 1 through 7 from Table 3.

Step 1: Formulate Review Question

A systematic review usually sets out to answer a question comparing one treatment with another (including success rates and complications) or to look at how exposure leads to disease. To define the research question one is interested in, one should ask four key questions about the purposed study:

- What is the population of interest?
- What interventions are being considered?
- What are the outcomes of interest?
- What study designs are appropriate to answer this question?

As these questions are answered, the scope of the review is defined, and the inclusion and exclusion criteria become self-evident. Let's consider the example of limb salvage for severe open tibial fractures, a topic recently addressed in a systematic review from our institution.[12] For this study, the review question was: "Considering patients with severe open tibial fractures, which option (amputation versus salvage) provides the lowest complication rates, quickest return to work, and best quality of life?"

Table 3. Steps in Conducting a Systematic Review*

Step	Components
1. Formulate review question	
2. Define inclusion and exclusion criteria	Participants Interventions and comparisons Outcomes Study designs and methodological quality
3. Locate studies	Develop search strategy considering: The Cochrane Controlled Trials Register(CCTR) Electronic databases and trials registers not covered by CCTR Checking of reference lists Hand searching of key journals Personal communication with experts in the field
4. Select studies	Have eligibility checked by more than one observer Develop strategy to resolve disagreements Keep log of excluded studies, with reasons for exclusions
5. Assess study quality	Consider assessment by more than one observer Use simple checklists rather than quality scales Always assess concealment of treatment allocation, blinding, and handling of patient attrition Consider blinding of observers to authors, institutions, and journals
6. Extract data	Design and pilot data extraction form Consider data extraction by more than one observer Consider blinding of observers to authors, institutions, and journals
7. Analyze and present results	Tabulate results from individual studies Examine forest plot Explore possible sources of heterogeneity Consider meta-analysis of all trials or subgroups of trials Perform sensitivity analyses, examine funnel plots Make list of excluded studies available to interested readers
8. Interpret results	Consider limitations, including publication and related biases Consider strength of evidence Consider applicability Consider numbers needed to treat to benefit/harm Consider economic implications Consider implications for future research

*Egger M, Smith GD. Principles of and procedures for systematic reviews. In: Egger M, Smith GD, Altman DG, eds. *Systematic Reviews in Health Care: Meta-Analysis in Context.* 2nd ed. London: BMJ Publishing Group; 2001:23–42.

Step 2: Define Inclusion and Exclusion Criteria

As the research question is developed, the focus of the question determines the inclusion and exclusion criteria. If the question is too narrow, too few studies may be included, yielding a review with very low precision. If the question, on the other hand, is too broad, it will capture many more

studies than is ideal, and one might lose the ability to detect differences in subgroup analysis.

Table 4 lists specific inclusion and exclusion criteria from the example study on limb salvage. Note that some of the criteria are very specific, helping to limit the scope of the review, so the studies included will directly help answer the review question. The decision was made to include prospective and retrospective observational studies in this review but not case series, technique, or review articles.

Step 3: Locate Studies

For any systematic review, the literature search employed must be both comprehensive and reproducible. In theory, the search should uncover all existing studies concerning the topic of interest. If studies are omitted, bias can be introduced. Some reasons for omissions include inadequate search criteria, inaccurate indexing of articles, and inaccessibility of some journals. The exact search process needs to be meticulously documented so that the search is both transparent and reproducible. This allows the search to be easily verified or updated in the future.

Traditionally, MEDLINE and EMBASE have been the primary resources for searching the medical literature. MEDLINE indexes primarily U.S. (and primarily English-language) journals; EMBASE has better European (and non–English-language) journal coverage. Overlap between these two databases is around 20 to 30 percent. Although these "traditional" databases may still be useful for identifying recently published studies, there is a more comprehensive resource for identifying published clinical trials: The Cochrane Central Register of Controlled Trials (CENTRAL).[31]

Formerly known as the Cochrane Controlled Trials Register (CCTR), CENTRAL now contains hundreds of thousands of records, making it the best single source of published trials available. This massive resource has been compiled by the Cochrane Collaboration (www.cochrane.org) and is continuously updated as new studies are published and as older studies are identified and indexed by their reviewers.[32]

In addition to the electronic databases, a thorough literature search should expand to other sources via hand searching (Table 5).[33] This includes reviewing reference lists from textbooks, narrative reviews, or expert opinion papers on the topic of interest. In addition, conference proceeding and clinical trial registries can be examined to help discover unpublished data or data pending publication. This combination of endeavors should produce a comprehensive list of article to be reviewed.

Table 4. Example of Inclusion and Exclusion Criteria (Limb Salvage)*

Inclusion Criteria	Exclusion Criteria
Primary data from prospective and retrospective observational studies	Review, technique, or case report articles
Human studies	Studies in which subjects are selected based on outcome (e.g., assessing only tibial fractures with nonunion)
Studies that include and stratify results for patients with type IIIB or IIIC open tibial fractures resulting from acute trauma	Studies with fewer than 20 total patients with type IIIB or IIIC open tibial fractures as a result of acute trauma
Studies that stratify results based on management of the above injuries by either primary amputation or limb salvage	Articles focused solely on children (younger than 18 yr) or elderly (older than 60 yr)
	Articles using the same patient data reporting on nondistinct outcomes
	Studies with nonstandard reconstructive techniques
	Studies with no relevant extractable outcomes

*Saddawi-Konefka D, Kim HM, Chung KC. A systematic review of outcomes and complications of reconstruction and amputation for type IIIB and IIIC fractures of the tibia. *Plast Reconstr Surg.* 2008;122:1796–1805.

Step 4: Select Studies

At this step, the inclusion and exclusion criteria are applied to the list of located articles. This is typically done in several stages. First, a review of the article titles is performed to select all studies that may potentially meet the inclusion criteria. Along the way, duplicate articles will be identified and eliminated.

Next, the abstracts of the studies identified in the title search are obtained and reviewed. Once again, studies that meet the inclusion criteria are identified, and others are eliminated.

Table 5. Resources for Locating Studies for Systematic Reviews

Electronic databases
- CENTRAL (The Cochrane Central Register of Controlled Trials)
- MEDLINE
- EMBASE

Hand searching
- Non-indexed journals
- Non-indexed databases (AMED, BIOSIS, CINAHL, and others)
- Textbook references
- Narrative review references
- Expert opinion references
- Conference proceedings
- Registries of unpublished or ongoing studies

Studies whose abstracts meet the inclusion criteria are retrieved, and the full text is analyzed. At this final stage, articles are eliminated based on exclusion criteria.

In theory, all of these stages should be performed independently by at least two qualified expert reviewers. Interrater agreement can be measured statistically by Cohen's kappa coefficient. Disagreements between reviewers can be settled by consensus agreement to help maximize reliability and reproducibility. This approach minimizes biases and omissions.[2]

Authors should track and report the number of articles at each step, and these data should be portrayed in a figure such as the one in our example (Fig. 2). At the final stage (full text review), it is helpful to report the number of articles eliminated by each of the exclusion criteria, to make this process transparent to the reader.

Step 5: Assess Study Quality

It is important to assess the quality of the individual studies selected, as flaws in those studies could distort the results of the meta-analysis or systematic review. There is, however, considerable debate over how this should be done.[34] Studies may be given a summary score based on overall quality, and these scores can be used to help weight the studies in terms of clinical significance. Many of these so-called "composite scales" have been developed, reflecting the controversy in this area.[35] Most scoring systems that have been developed are for randomized controlled trials; no scoring systems have been developed for retrospective studies. Use of a single composite score to represent study quality can be problematic, however, as selection of one scale over another has been shown to change the results of meta-analysis.[36]

Recently, a group of international guideline developers has put forth a new scoring system, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.[37] This system offers several potential advantages over other systems (Table 6). In the GRADE system, quality of evidence (high, moderate, low, and very low) is reported separately from the grades of recommendations (strong or weak).

Due to the perceived flaws in many of the composite scoring systems, analysis of individual components of study quality has been advised by some experts in the field.[38] This method avoids

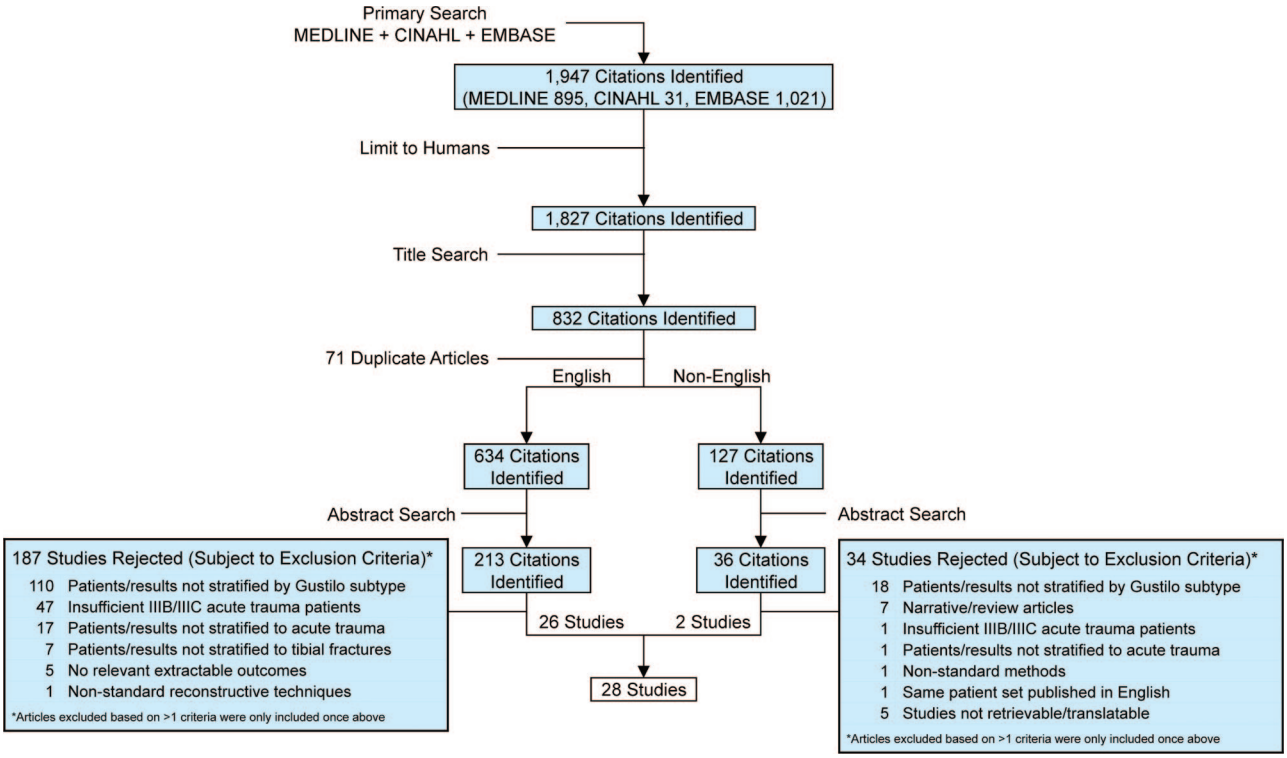

Fig. 2. Study attrition diagram (limb salvage). From Saddawi-Konefka D, Kim HM, Chung KC. A systematic review of outcomes and complications of reconstruction and amputation for type IIIB and IIIC fractures of the tibia. *Plast Reconstr Surg.* 2008;122: 1796–1805.

Table 6. GRADE Advantages*

Developed by a widely representative group of international guideline developers
Clear separation between quality of evidence and strength of recommendations
Explicit evaluation of the importance of outcomes of alternative management strategies
Explicit, comprehensive criteria for downgrading and upgrading quality of evidence ratings
Transparent process of moving from evidence to recommendations
Explicit acknowledgment of values and preferences
Clear, pragmatic interpretation of strong versus weak recommendations for clinicians, patients, and policy makers
Useful for systematic reviews and health technology assessments, as well as guidelines

*From Guyatt GH, Oxman AD, Vist GE, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336:924–926.

Table 7. Data Items Extracted: Limb Salvage Study*

Study design
Patient demographics
Outcomes:
Mean follow-up time
Duration of hospital stay
Complications
Rehabilitation time
Quality of life
Limb function
Pain
Return to work

*From Saddawi-Konefka D, Kim HM, Chung KC. A systematic review of outcomes and complications of reconstruction and amputation for type IIIB and IIIC fractures of the tibia. *Plast Reconstr Surg.* 2008;122:1796–1805.

some of the pitfalls of composite scales but can be more labor intensive.

Regardless of whether a composite scale or component analysis is used, the assessment of study quality is typically used to weight individual studies during pooling of the data. This should be done with caution, as there are several potential problems with this approach. For instance, although their influence may be reduced by giving them less weight, the results of poor studies may still be included in the analysis and influence results. The ideal approach may be to use sensitivity analysis to determine the effect of the individual components of study quality on the overall result of the systematic review.[38]

Step 6: Extract Data

This step requires time, concentration, and meticulous accuracy. The list of data to be extracted should be agreed upon during the design phase of the study. The primary focus of the data collected should be that which is required to prove or disprove the a priori hypothesis. Of course, additional data may be extracted, and additional associations may be explored after testing the a priori hypothesis. One must keep in mind, however, that positive associations can present themselves randomly; therefore, while searching for large numbers of associations, one might find something significant by chance alone.

The best way to be consistent in this process is to use a carefully designed form to enter the data as they are extracted from each study. Ideally, this

Table 8. Summary of Extracted Data (Limb Salvage)*

	Salvaged Limbs (range), No. of Patients Included	Amputated Limbs (range), No. of Patients Included
Length of hospital stay	56.9 days (25–129 days), 281	63.7 days (28–101 days), 88
Complications		
Secondary amputation	7.3% (0–27%), 1239	N/A
Osteomyelitis	17.9% (4–56%), 798	6% (6%), † 18
Nonunion	15.5% (0–50%), 777	N/A
Complete flap loss	5.8% (0–15%), 601	N/A
Secondary revision	N/A	33% (33%), † 18
Other clinical outcomes		
Superficial infection	8% (6–13%), 238	N/A
Donor-site morbidity	15% (11–17%), 99	N/A
Rehabilitation time		
Time to union	10.2 mo (7.9–12.3 mo), 430	N/A
Time to full weight bearing	8.1 mo (3.6–13 mo), 176	6 mo (6 mo), † 18
Return to work		
Percentage who returned to work	63.5% (19–100%), 432	73% (50–100%), 59
Delay until working for those who did return to work	14.4 mo (12.1–19.0 mo), 93	13.6 mo (10.0–15.8 mo), 31

N/A, not available.
*From Saddawi-Konefka D, Kim HM, Chung KC. A systematic review of outcomes and complications of reconstruction and amputation for type IIIB and IIIC fractures of the tibia. *Plast Reconstr Surg.* 2008;122:1796–1805.
†Reflects data from only one study.

process should be blinded as to the authors and the sources of each article to avoid bias. Data that are typically extracted include study characteristics, sample demographics, and outcomes data. The data extracted from each study in our limb salvage example are presented in Table 7.[12]

If practical, this process should be repeated with two or more researchers so that there is a consensus of the extracted data. Once again, interrater reliability can be assessed with Cohen's kappa coefficient. An alternative to this would be to conduct random audits of the process. For example, a random sample of the studies could be reexamined by an independent investigator to confirm accurate data extraction.

Step 7: Analyze and Present Results

At this point, the data can be pooled if appropriate and presented as a summary outcome or

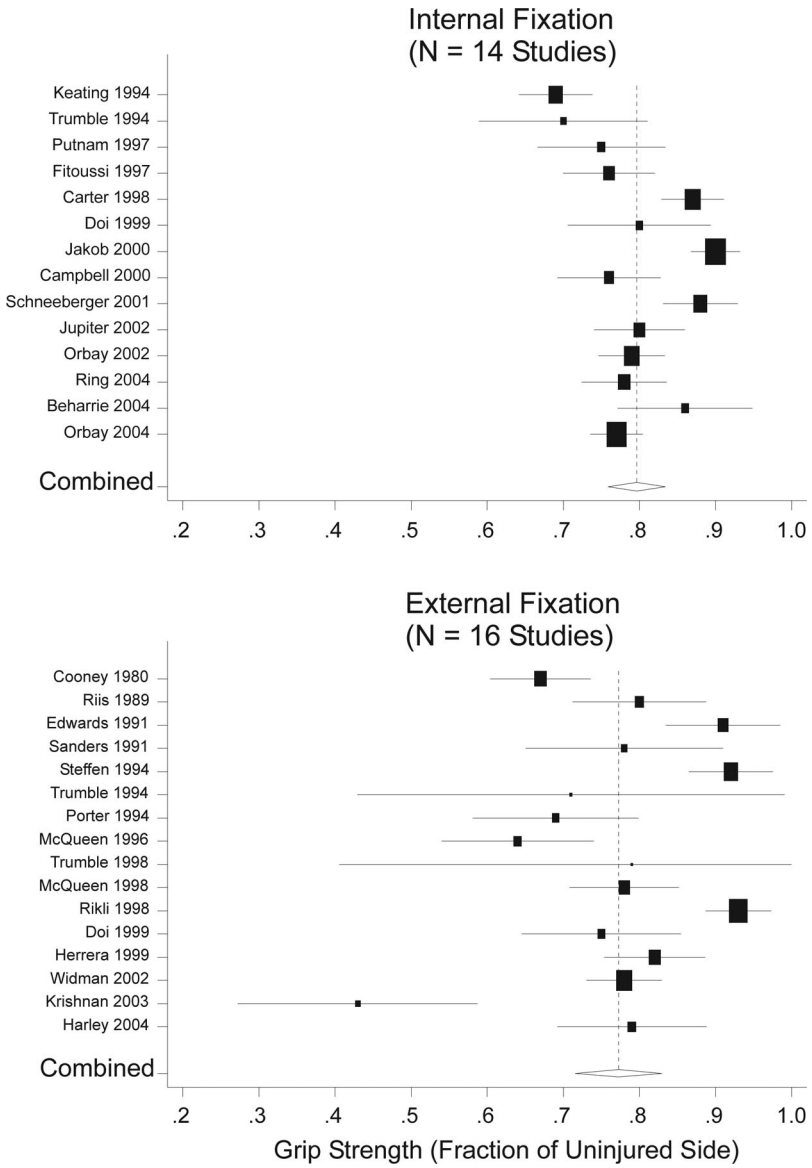

Fig. 3. Forest plot (distal radius example). This is taken from a meta-analysis of distal radius fracture fixation techniques. Mean grip strength as a fraction of the contralateral uninjured handgrip strength and 95 percent confidence intervals are plotted for external fixation along with the combined meta-analytic mean. *Box size* represents the relative weight used for meta-analytic pooling based on the inverse of the standard error of the mean.[39]

effect, and meta-analysis can be performed if indicated. Conceptually, meta-analysis combines the results of similar studies of a particular intervention, taking into account measures of variability within and between the studies, to improve the validity of the conclusion. If the studies that are being reviewed have a high degree of heterogeneity, the author may not be able to combine the data, and a meta-analysis should not be performed but rather a narrative summary given instead.

In our limb salvage example, the outcomes data that were extracted were not reported consistently using standardized measures, so meta-analysis was not possible. Data were, however, able to be extracted and summarized to effectively compare the two outcomes of interest: limb salvage versus amputation (Table 8).[12]

Presentation of the data should include a tabulation of the results from the individual studies. Ideally, a forest plot should be used to compare the results of the individual studies (Fig. 3). This type of graph shows not only the data extracted from individual studies, but also a representation of the statistical weight of each study, with regard to confidence intervals and standard error of the mean.

Formal guidelines exist regarding the reporting of systematic reviews. Each of these guidelines is in the form of a checklist: a list of items that should be included whenever reporting a systematic review. The MOOSE report gives a detailed checklist (Table 9) for reporting meta-analyses of observational studies.[4] The PRISMA checklist[3] (Table 10) pertains to meta-analyses of randomized controlled trials; this set of guidelines replaces the older Quality of Reporting of Meta-analyses (QUOROM) guidelines.[9] An exhaustive explanation and elaboration of the PRISMA guidelines has been published for the interested reader.[40]

Step 8: Interpret Results

Finally, a systematic review should interpret the results that have been presented. This should include a discussion of the limitations of the study, including potential biases in the original articles, as well as biases that may have influenced the review itself (Table 4). Also, the strength of the evidence should be reviewed; strength and applicability of the review findings will depend on the data upon which it is based. Finally, directions for future research will be evident, especially if the review has discovered a significant heterogeneity between the studies on the topic of interest.

Table 9. MOOSE Checklist for Meta-Analyses of Observational Studies*

Reporting of background should include:
Problem definition
Hypothesis statement
Description of study outcome(s)
Type of exposure or intervention used
Type of study designs used
Study population
Reporting of search strategy should include:
Qualifications of searchers (e.g., librarians and investigators)
Search strategy, including time period included in the synthesis and keywords
Effort to include all available studies, including contact with authors
Databases and registries searched
Search software used, name and version, including special features used (e.g., explosion)
Use of hand searching (e.g., reference lists of obtained articles)
List of citations located and those excluded, including justification
Method of addressing articles published in languages other than English
Method of handling abstracts and unpublished studies
Description of any contact with authors
Reporting of methods should include:
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested
Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)
Documentation of how data were classified and coded (e.g., multiple raters, blinding, and interrater reliability)
Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate)
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results
Assessment of heterogeneity
Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated
Provision of appropriate tables and graphics
Reporting of results should include:
Graphic summarizing individual study estimates and overall estimate
Table giving descriptive information for each study included
Results of sensitivity testing (e.g., subgroup analysis)
Indication of statistical uncertainty of findings
Reporting of discussion should include:
Quantitative assessment of bias (e.g., publication bias)
Justification for exclusion (e.g., exclusion of non–English-language citations)
Assessment of quality of included studies
Reporting of conclusions should include:
Consideration of alternative explanations for observed results
Generalization of the conclusions (i.e., appropriate for the data presented and within the domain of the literature review)
Guidelines for future research
Disclosure of funding source

*From Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting: Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008–2012.

Table 10. PRISMA Checklist for Meta-Analyses of Randomized Controlled Trials*

Section/Topic	No.	Checklist Item
Title		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
Abstract		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
Introduction		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
Methods		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, metaregression), if done, indicating which were prespecified.
Results		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (1) simple summary data for each intervention group and (2) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).
Additional analysis	23	Give results of additional analyses, if done [e.g., sensitivity or subgroup analyses, meta-regression (see item 16)].
Discussion		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias) and at review level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
Funding		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

*From Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62:1006–1012.

USING SYSTEMATIC REVIEWS IN CLINICAL PRACTICE

Using high-level evidence from systematic reviews to treat individual patients at the bedside represents the pinnacle of evidence-based medicine. Several key questions should be considered before applying the results of systematic reviews to individual patients.[41]

1. *Does this evidence apply to this particular patient?* One should consider the disease pathogenesis and patient-specific factors as well as any differences in environmental factors when answering this question. Your patient may not have to meet all the inclusion and exclusion criteria for a particular study's results to be applicable. Remember that differences between your own patients and those in trials tend to be quantitative (e.g., matters of degree in risk and responsiveness) rather than qualitative (no response or adverse response).[42]
2. *Is this intervention feasible for this particular patient?* Regional differences in the availability and affordability of a given intervention will influence its use in individual patients. One should also consider whether the required experience or expertise is available in the region to effectively administer the intervention and/or monitor its results over time.
3. *What is the risk:benefit ratio for this particular patient?* If the results of the systematic review seem both applicable *and* feasible, one must still consider if the benefits outweigh the risks for this individual patient. The overall estimate of clinical effect must be derived from the article, and that result extrapolated to the individual patient. A statistical analysis could take the form of a "number needed to treat" calculation, the scope of which is beyond this article.[41]
4. *What are the values and preferences of this particular patient?* Finally, we should not base treatment decisions on laboratory results or radiographs, but on the patient as an individual. Patients have innate values and preferences that should be considered in making all treatment decisions.

CONCLUSIONS

Systematic reviews can help us synthesize information, improve the significance of data from smaller studies, and identify areas where further research is required. They are an important tool to help us practice evidence-based medicine in this modern age. This article provides a step-by-step guide to conducting a proper systematic review, including new guidelines not covered in previous reports on this topic.[2,43] Results, however, may be biased despite careful methodology, and application of findings to individual patients will always require thoughtful analysis by the physician providing care.

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