Evidence-Based Medicine and The Cochrane Collaboration


Abstract
Providing evidence-based care to patients involves turning a clinical problem into an answerable question, systematically searching for the best evidence relevant to the question, critically appraising that evidence, and, finally, using the evidence as the basis for clinical decisions to solve the problem. While the overload of medical information today presents a demanding challenge to physicians to sort and identify relevant and valid evidence, it is vitally important to translate that evidence into clinically useful terms. To apply evidence to patient clinical management, it is critical to discuss with patients the evidence, the benefits and the harms, and the alternative treatments, such that they understand and can fully participate in the decision-making process. The framework of evidenced-based medicine provides a concrete methodology to address these issues, here, framed and detailed in five steps. The Cochrane Collaboration has been at the forefront of applying the methods of evidence-based medicine (EBM) in the treatment and management of musculoskeletal and other disorders.

Clinicians are confronted with information overload and the need to identify relevant evidence to incorporate into clinical practice. The Cochrane Library is one of the fastest and most reliable sources of the best evidence for therapy on which to base clinical decisions. OMERACT (Outcome Measures in Rheumatology) is linked to the Cochrane Musculoskeletal Group (CMSG), one of the international groups of The Cochrane Collaboration, where the outcomes endorsed by OMERACT, based on truth, discrimination, and feasibility (OMERACT filter), are recommended for use in systematic reviews of interventions for musculoskeletal conditions. The five steps of EBM provide a useful framework to improve the incorporation of the best evidence in clinical practice.

What is Evidence-Based Medicine?
Evidence-based medicine (EBM) is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research and patients’ values and expectations.

Providing evidence-based care to patients involves turning a clinical problem into an answerable question and then systematically searching for the best evidence, critically appraising the evidence, and using the evidence as the basis for clinical decisions to solve the problem.

The Need for Evidence-Based Medicine
Clinical decisions can benefit from current practice guidelines based on the best possible evidence; today, these decisions and guidelines are increasingly evidence-based. Sources currently abound for information on trials and investigations: PubMed is a service of the U.S. National Library of Medicine (NLM) that includes over 18 million journal citations from MEDLINE (NLM’s database) and other life science journals for biomedical articles. Each year, MEDLINE indexes over 500,000 newly published articles, and Cochrane Central adds about 20,000 newly published randomized trials. There are approximately 1500 new articles and 55 new trials per day. Consequently, clinicians
are confronted at times with information overload when trying to identify relevant evidence to incorporate into clinical practice. Their decisions are often out of date with current evidence and guidelines; hence, patients are denied the benefits of new therapeutic options. It took over 10 years for the implementation of thrombolytic therapy for myocardial infarction in clinical practice after evidence from randomized clinical trials and systematic reviews were published. Easier access to the results of research is clearly needed so as to incorporate best evidence sooner into clinical practice.

The Cochrane Library provides a source of evidence that is easily searchable and has a large number (3625) of reviews and broad topic areas, and it provides summary of findings tables with details of likely effects in specific populations. The Cochrane Collaboration is an international not-for-profit and independent organization, dedicated to making up-to-date, accurate information about the effects of health care readily accessible worldwide. It produces and disseminates systematic reviews of health care interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions. The Cochrane Collaboration was founded, in 1993, and named after the British epidemiologist, Archie Cochrane. The Cochrane logo (Fig. 1) illustrates the global objectives of the group and key scientific processes. It shows the results of a systematic review of RCTs of a short, inexpensive course of a corticosteroid given to females about to give birth too early. The first of these RCTs was reported in 1972. The diagram summarizes the evidence that would have been revealed had the available RCTs been reviewed systematically. A decade later, it indicates strongly that corticosteroids reduce the risk of babies dying from the complications of immaturity by 30% to 50%. Because no systematic review of these trials were published until 1989, most obstetricians did not realize that the treatment was so effective. As a result, tens of thousands of premature babies suffered and died unnecessarily (and needed more expensive treatment than was necessary). This is just one of the many examples of the human costs resulting from failure to perform systematic, up-to-date reviews of RCTs of health care.

The Cochrane Collaboration continues to pursue its mission of preparing, maintaining, and promoting access to systematic reviews. Recent methodological advances have increased the usability and usefulness of evidence from Cochrane reviews in making well-informed decisions in health care. Free online access to the Cochrane Library exists in certain countries and geographic regions through a special scheme. Negotiations are underway for free access in other places.

The CMSG, one of 52 international groups in the Cochrane Collaboration, has completed 111 reviews and 84 protocols, now in the Cochrane Library. These systematic reviews synthesize the results of high quality studies to determine the effectiveness and safety of interventions for the prevention, treatment, and other aspects of management of musculoskeletal diseases, including gout, Legg-Calvé-Perthes disease, systemic lupus erythematosus (SLE), osteoarthritis (OA), osteoporosis, pediatric rheumatology, rheumatoid arthritis, soft tissue rheumatism (fibromyalgia, upper limb conditions, lower limb conditions), spondyloarthritis, systemic sclerosis, and vasculitis.

OMERACT

OMERACT (Outcome Measures in Rheumatology) is linked to the CMSG, where the outcomes endorsed by OMERACT are recommended for use in Cochrane systematic reviews. OMERACT was started, in 1992, as a transatlantic effort to agree on a core set of outcomes for rheumatoid arthritis trials. It expanded into other fields and areas (safety, economics, imaging, and biological markers), study types (longitudinal observational studies), other diseases (osteoarthritis, osteoporosis, ankylosing spondylitis, systemic lupus erythematosus, fibromyalgia) and became patient-inclusive.

The process to define outcome measures is data-driven, iterative, and prepared by small expert working groups, including rheumatologists, health professionals, trialists, methodologists, scientists from industry, regulators, and patients. A final consensus is formulated based on all participants’ views and preferences.

To be applicable in its intended setting, a measure must be truthful, discriminative, and feasible. This is known as the OMERACT filter. Each word represents a question to be answered of the measure, in each of its intended settings:

- Truth. Is the measure truthful, does it measure what is intended? Is the result unbiased and relevant? The word captures issues of face, content, construct, and criterion validity.
- Discrimination. Does the measure discriminate between situations of interest? The situations can be states at one time (for classification or prognosis) or states at different times (to measure change). The word captures issues of reliability and sensitivity to change.
- Feasibility. Can the measure be applied easily, given constraints of time, money, and interpretability? The word captures an essential element in the selection of
measures, one that may be decisive in determining a measure’s success.

To support clinical decision-making, a balanced assessment of outcomes for both benefit and harm is needed in order to arrive at the best evidence for therapeutic interventions. Although randomized controlled trials are considered the gold standard for evaluating therapeutic interventions and to provide the best evidence, they may not adequately address rare and delayed adverse effects. EBM suggests several frameworks of evidence, specific for each type of clinical question. Study designs to assess benefit or harm are not limited to controlled trials, for example, the evidence for the use of hip replacement as a dramatically effective intervention for patients with disabling osteoarthritis of the joint was provided by case series.

Practicing Evidence-Based Medicine

An EBM approach can be used to solve problems related to the diagnosis, prognosis, or management of a case. The Cochrane Collaboration has focused upon therapy but is developing approaches to diagnosis and prognosis. A useful approach is to follow five steps when applying EBM in practice. Using cyclo-oxygenase-2 inhibitors (coxibs) and biologics let us use these five steps to look at some issues in evidence based rheumatology/medicine using the clinical case outlined below.

Clinical Scenario

Mrs. S, aged 48 years, developed symmetric polyarthritis of her wrists, finger joints, knees, and ankles 6 months ago. She has early rheumatoid arthritis. She showed some improvement with nonsteroidal anti-inflammatory drugs (NSAIDs) and methotrexate, but after 6 months, she continued to have persistent disease activity and developed radiological erosions. NSAIDs can partially control joint inflammation and pain, but they do not modify the natural course of rheumatoid arthritis. The patient had heard about biologics and asked her physician what the benefit and safety is likely to be for her.

Step 1 – Formulating a Clinical Question

Clinical questions are generated from clinical problems and are usually related to diagnosis, etiology, prognosis, or treatment or prevention. The importance of a question varies according to the perspective of the person asking it. The introduction of new treatments leads to questions such as those related to efficacy and safety.

This patient scenario generates potential questions, for example: “Should patients with early rheumatoid arthritis be treated with a biologic agent? What is the evidence that a biologic reduces joint damage in patients where NSAIDS and methotrexate do not?”

A well-built clinical question should have four components that can be identified by the acronym PICO:

- P for patient population: A description of the patient or the target disorder of interest.
- I for intervention: Could include an exposure, a diagnostic test, a prognostic factor, therapy, or patient perception, etc.
- C for comparison intervention: Could be a placebo or active treatment.
- O for outcome: A clinical outcome of interest to you and your patient.

Looking at our case scenario:


Intervention: A biologic agent.

Comparison intervention: NSAIDs, including coxibs; methotrexate could be continued, as it did provide some benefit or be stopped.

Outcome: Reduction of joint damage.

Clinical question would be: In a 48-year-old female, with early rheumatoid arthritis, can a biologic agent reduce joint damage, compared to NSAIDS and including coxibs?

Step 2 – Searching for the Best Evidence

The next step in EBM methods is searching for the best evidence available. Clinicians have the responsibility of seeking the best evidence to guide their practice. The clinical problem should guide the nature and source of evidence to be sought, rather than habits and traditions. Unfortunately, most clinical guidelines and practice recommendations are not based on the most up-to-date evidence available; therefore, clinicians need effective searching skills and easy access to bibliographic databases.

There are two sources of evidence: primary and secondary sources. Primary literature can be searched in Google and on electronic databases, such as MEDLINE, EMBASE, for relevant journals, reference lists, and conference proceedings; similarly, printed materials can be accessed in libraries from indexed sources; drug companies may be contacted; grey literature can be searched; personal communications can be sent. However, there are over 18 million journal citations in MEDLINE, which is an unmanageable amount of information to explore.

Secondary or pre-appraised literature, such as systematic reviews, help make sense of unmanageable amounts of research, bringing together separately conducted studies and synthesizing their results. The Cochrane Library is an outstanding source of the most reliable, independent evidence on which to base clinical treatment decisions, as Cochrane reviews are produced to the highest methodological standard. Cochrane reviews are done on a variety of health care diseases and conditions, including musculoskeletal conditions. Cochrane reviews have been recommended as a good source of pre-appraised information for EBM practice.

A search in MEDLINE using publication types for randomized controlled trials and meta-analyses from January 2008 to January 2009 found there were 105 randomized controlled trials and 19 meta-analyses on rheumatoid arthritis.
Hence, there was approximately five times more primary literature than secondary literature on rheumatoid arthritis within the last year.

Other sources of pre-appraised literature are EBM journals (ACP Journal Club, EBM Journal) and the series of BMJ books that are based on Cochrane reviews (Table 1).

Systematic reviews in the Cochrane Library can be accessed by browsing or searching. You can browse by topic or by review groups or do a search using the title, abstract, or keywords. For our case scenario, a search by topic revealed six reviews on biologics for treating rheumatoid arthritis that included etanercept and infliximab.

**Step 3 – Critical Appraisal of the Evidence**

The appropriate information from the search is then selected for critical appraisal to evaluate the validity and usefulness of the evidence. Good medical research must have sufficient methodological rigor to be reliable enough to answer clinical questions. A simple method to appraise evidence will involve asking the following questions:

1. **Is the review valid?**
   a. Does the review address the components of the clinical question?
      i. Were there clearly defined groups of patients, similar in all important ways other than exposure to the treatment or other cause?
      ii. Were treatments, exposures, and clinical outcomes measured in the same ways in both groups? (Was the assessment of outcomes either objective or blinded to exposure?)
      iii. Was the follow-up of the study patients sufficiently long (for the outcome to occur and complete)?
      iv. What study designs were included?
   b. METHODS: Assessment of risk of bias in included studies
      i. Was the allocation sequence adequately generated?
      ii. Was allocation adequately concealed?
      iii. Was knowledge of the allocated interventions adequately prevented during the study?
      iv. Were incomplete outcome data adequately addressed?
      v. Are reports of the study free of suggestion of selective outcome reporting?
      vi. Was the study apparently free of other problems that could put it at a risk of bias?

In Cochrane reviews, the assessment of risk of bias may be presented in a usable format, as shown in Figure 2 for the Cochrane review, “Etanercept for the Treatment of Rheumatoid Arthritis.” This is a “risk of bias summary” figure, presenting all of the judgments in a cross-tabulation of study by entry in the tool. A judgment of “Yes” for low risk of bias is represented by a green dot, a judgment of “No” for high risk of bias is represented by a red dot, and a judgment of “Unclear” is represented by a yellow dot.

The review has a low risk of bias. It addressed the components of our clinical questions and included randomized clinical trials with very low risk of bias, as there are very few red dots in Figure 2, compared to green dots.

2. **What are the results?**

The evidence showed that 80% of those on etanercept (25 mg twice weekly for 12 months) had no progression to joint damage, compared to 58% of those on control or

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**Table 1** BMJ Books Based on Cochrane Reviews

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<tr>
<th>Number</th>
<th>Title</th>
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<tbody>
<tr>
<td>1.</td>
<td>Clinical Evidence</td>
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<td>2.</td>
<td>Evidence Based Cardiology</td>
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<tr>
<td>3.</td>
<td>Evidence Based Dermatology</td>
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<tr>
<td>4.</td>
<td>Evidence Based Gastroenterology and Hepatol</td>
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<td>5.</td>
<td>Evidence Based Hypertension</td>
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<td>6.</td>
<td>Evidence Based Infectious Diseases</td>
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<td>7.</td>
<td>Evidence Based Pediatrics and Child Health</td>
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<td>8.</td>
<td>Evidence Based Practice in Primary Health</td>
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<td>9.</td>
<td>Evidence Based Rheumatology</td>
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<td>10.</td>
<td>Evidence Based Sports Medicine</td>
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<td>11.</td>
<td>Evidence Based Oncology</td>
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<td>12.</td>
<td>Evidence Based Ophthalmology</td>
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<tr>
<td>13.</td>
<td>Evidence based Paediatric Oncology</td>
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**Figure 2** Methodological quality summary: review authors’ judgments about each methodological quality item for each included study. Circles with “+” are green, “?” are yellow, and “-” are red.
placebo, giving an absolute risk difference of 22%. The number of patients needed to treat (NNT) with etanercept to achieve a favorable outcome of no progression to joint damage was five. This NNT depends on the baseline risk of progression to joint damage of 42%, which is the average baseline risk in these clinical trials, conducted mostly in specialty clinics. For people at a lower risk of joint damage, the NNT would be higher; for example, if only 20% are at risk of progressing to joint damage, the NNT would be 13.

The same systematic review also found that the absolute risk difference for ACR50 was 35% (39.4% in the treatment group, compared to 4.5% in the control group), and the number needed to treat to achieve an ACR50 was three, given a baseline risk of achieving ACR50 without treatment of 4.5%.

The absolute difference and the NNT depend on the baseline risk of the patient population considered. Fewer patients will need to be treated for one to benefit in a group of patients with a higher risk than in a group of patients with a lower risk. This patient fits the profile of the patients in the trials, so this NNT is reasonable.

One of the objectives of Cochrane reviews is to provide the findings in a systematic style that can be easily understood and be more usable for all target audiences: clinicians, decision-makers, and consumers. Physicians are more likely to recommend starting therapy when only given the relative risk information compared to the number needed to treat. In the Health Information Project: Presentation Online (HIPPO) trial, similar results were found—relative risk reduction (RRR) was more persuasive than absolute risk reduction (ARR), NNT, and percent of event-free patients. This means that relative risk reduction can be misleading, particularly when event rates are low, since a large relative risk reduction can accompany a small absolute risk difference.

The target audiences often prefer percentages as a clinically useful format in comparison to absolute measures and NNT, as well as to verbal and graphical formats. However, another meaningful expression of active treatment over control mentioned above, is the number needed to treat to benefit or harm \[1/\text{ARR} = 1/(\text{Pc} – \text{Pi})\].

Overall, findings were presented as clinical relevance tables in reviews of the CMSG. With recent methodological updates in the Cochrane Collaboration as a whole, summary of findings tables are being adopted as a way to present results. Summary of findings tables are important as they present key information in a systematic way, providing both absolute and relative risk for the most important outcomes, as well as the quality of evidence (defined as the extent to which confidence in an estimate of the effect is adequate to support recommendations). The CMSG is suggesting that NNT be included in the tables.

3) Are the results valid?

There are two methods for evaluating evidence in the reviews of the CMSG. The Cochrane Collaboration recently adopted the GRADE (Grading of Recommendations Assessment Development and Evaluation) approach, which specifies four levels of quality (high, moderate, low, and very low), where the highest quality rating is for a body of evidence based on randomized trials without important limitations. Review authors can downgrade randomized trial evidence depending on the presence of five factors (study limitations, inconsistency of results, indirectness of evidence, imprecision, and publication bias) and upgrade the quality of evidence of observational studies depending on three factors (large magnitude of effect; plausible confounding, which would reduce a demonstrated effect; and dose-response gradient). Table 2 shows the factors and consequences of the GRADE approach.

### Table 2: GRADE Approach for Grading Quality of Evidence

<table>
<thead>
<tr>
<th>Factors That Can Reduce the Quality of the Evidence</th>
<th>Consequence</th>
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<tbody>
<tr>
<td>Study limitations</td>
<td>Down 1 or 2 levels</td>
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<tr>
<td>Inconsistency of results</td>
<td>Down 1 or 2 levels</td>
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<tr>
<td>Indirectness of evidence</td>
<td>Down 1 or 2 levels</td>
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<tr>
<td>Imprecision</td>
<td>Down 1 or 2 levels</td>
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<tr>
<td>Publication bias</td>
<td>Down 1 or 2 levels</td>
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<table>
<thead>
<tr>
<th>Factors That Can Increase the Quality of the Evidence (If Study Meets All Previous Five Factors)</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large magnitude of effect</td>
<td>Up 1 or 2 levels</td>
</tr>
<tr>
<td>All plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed</td>
<td>Up 1 level</td>
</tr>
<tr>
<td>Dose-response gradient</td>
<td>Up 1 level</td>
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**Step 4 – Applying Evidence to Patients**

The conclusions of this search and critical appraisal are worthwhile only if they are translated into actions that af-
Clear data presentation is an important requirement for practicing EBM. It is important to translate the results into clinically useful terms. Five different ways to make evidence for therapy more user-friendly are described in the book Evidence Based Rheumatology and include:

1. Web availability.
2. Simple quality grading.
3. Use of percentages and NNT.
5. Patient handouts or decision-aids in 1, 5, 15, and 45-minute formats. Four versions of the same information from systematic reviews, presented in ever increasing detail and graded according to the level of evidence. They were developed by the Cochrane Musculoskeletal Consumer Group, Musculoskeletal Review Group, and Ottawa Health Decision Centre and are available on the Ottawa Health Decision Centre website.

To apply evidence to a patient clinical management, it is critical to discuss the evidence, the benefits and harms, and the alternative treatments with patients so that they understand. This process also involves exploring the patient’s values and beliefs, and can be facilitated by the use of visual aids, such as a graphical display of treatment effect (Fig. 3) and decision aids. Patient decision-aids present the treatments as a choice of options and include personalized information about outcomes, probabilities, and uncertainties in sufficient detail for decision-making. Decision-aids improve people’s knowledge of the options, create accurate risk perceptions of their benefits and harms, reduce difficulty with decision-making, and increase participation in the process. They also demonstrate reduced rates of elective invasive surgery in favor of conservative options. In Figure 3, each display represents a total of 100 people with rheumatoid arthritis.

Without treatment, five people will experience an ACR50 response (green faces); with treatment, 41 people will experience an ACR50 response (green plus yellow faces). Therefore, 36 more people will benefit from the treatment (yellow faces). A clinical decision is then made and applied, taking into account the patient’s preferences, values and situation. Patients’ preferences vary with the type of decision-aids; knowledge was found to increase when more detailed rather than simpler decision-aids were used. There was also greater agreement between their values and choice with more detailed decision aids.

**Step 5 – Self Evaluation**

The fifth step in practicing EBM is self evaluation. It involves evaluating your performance in:

- Asking answerable clinical questions.
- Finding the best evidence.
- Critically evaluating the evidence for its validity and potential usefulness.
- Integrating the critical appraisal with clinical expertise and applying the results in clinical practice.

Another step in the self evaluation process is considering your patient’s reactions or improved health care. This will be influenced by their participation in the decision-making process, their adherence to treatment, any adverse events they experience, and their general health status.
Conclusion
The practice of the five steps of EBM is a way forward to improve the incorporation of best evidence into clinical practice, as well as to maintain and expand clinically important knowledge. However, EBM principles and practice are not yet sufficiently disseminated, and there is also the challenge for clinicians to integrate it into routine clinical practice. The Cochrane Collaboration’s Database of Systematic Reviews alleviates the challenge, as it is one of the most reliable and quickly accessible sources of best evidence for therapy on which to base clinical decisions.

Disclosure Statement
None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

References
38. Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. Ann Intern Med.


