Module 4: Finding the Evidence: Individual trials

Certainly, if a practitioner is unable to uncover recent relevant systematic reviews on a topic, a thorough search of the primary literature for recent single studies is in order. However, even if spot-on systematic reviews are available, a quick search of the most recent literature is a good idea….just in case a new big trial has been published that may impact an answer to the clinical question.

Let's review the evidence hierarchy one last time. Since we are using a scenario involving therapy, randomized controlled trials are the type of single studies for which we need to look.

There are several resources at your fingertips that can be used to find single studies on a topic:

- PubMed ,of course, is the single largest database for clinical trials. As of March 2010, PubMed includes over ¼ million Randomized Controlled Trials. Please keep in mind that there are limits and filters, particularly Clinical Queries, to narrow your PubMed searches to specific study types.
- Although, PubMed covers much of the health-related literature, there are a few other lesser used resources to find good RCTs:
    - The Cochrane Central Register of Controlled Trials (or CENTRAL) is a hidden gem of a database. This database includes citations for over 600,000 clinical trials (mainly RCTs) used to create the Cochrane Systematic Reviews. It includes those published in conference proceedings and many other sources not currently listed in other bibliographic databases. If you have access to the Cochrane Library, CENTRAL database is located in the middle of the database list.
    - The TRIP internet database is an excellent free resource that scans the selected journals and important websites for reviews and primary research of good quality for clinical practice. Results of a search are categorized by evidence type. Most of the categories are fairly self-evident; however, the primary research needs some explanation.
        - Core primary research is content from the big 5 internal medicine journals (NEJM, JAMA, Lancet, BMJ and Annals of Internal Medicine) and from EvidenceUpdates, a collaboration between the BMJ and McMaster University's Health Information Research Unit, which rates articles from over 130 journals.
        - Extended primary research comes from a 'core' set of 300 journals identified by the editors as being the best for clinical topics.
    - Google scholar is a subset of Google. You are all, no doubt, aware that ANY Google searches result in thousands often millions of results. By using Google Scholar, one can limit those results to citations of health literature from scholarly publishers and educational or government websites and organizations. In addition, the underlying search algorithm works in a way that allows the best "evidence" to surface in the first few pages, so there is no need to view page after page after page of results. As with Cochrane's CENTRAL database, Google Scholar includes trial literature not always found in PubMed.

- There are other topic-based databases that may be worth a look depending on the subject of your scenario:
  - The CINAHL database – has excellent coverage of trials in the allied health fields and CAM.
  - PsychINFO has strong coverage in the psychology with some psychiatry topics
  - And SportsDiscus, as its name implies, covers the sports medicine literature

Of course the advantage of using systematic reviews to answer a question is that review authors and/or editors have taken on the burden of appraising the studies they've incorporated into the review. That burden, however, is transferred to you the reader if you use the evidence from single studies.

To facilitate this, you can turn to one of several appraisal check sheets available on the Internet. A particularly useful and common checklist is entitled: RAMMbo. RAMMbo is an acronym for the check sheet that helps readers appraise and assess the single studies.

- The R in RAMMbo stands for recruitment (did the recruited subjects in the study represent your patient?)
- A is Allocation – How did the researches allocate the groups. Were the groups similar at the onset? Were the assignments to the treatments randomized?
- The first M stands for Maintenance. Were the groups treated equally? Were outcomes obtained and analyzed for all participants?
- The second M stands for Measurements. Were the patients blinded to the treatment? Were the measurements objective and the same across the study?

As you might imagine, practicing clinicians do not have much time on their hands to analyze individual studies and often don not have enough confidence to apply the results to patient care. However, one CANNOT assume that studies published even in the best medical journals are properly conducted. A recent paper in JAMA highlighted the ominous incidence of improper, and at times unethical, reporting of results of clinical trials.

In this paper, researches reviewed 102 pre-clinical trial objectives (called protocols) and examined the outcomes researchers planned to measure. They then obtained the subsequent published articles reporting the results of the 102 trials. Researchers found that in 62% of the articles there was a discrepancy in what they said they were going to measure and what was published. They also found incomplete reporting of outcomes in a staggering 92% of the trials. And in 86%, the authors denied the existence of such unreported outcomes despite the evidence.

Also, the authors of this study have reported a strong bias towards statistically significant outcomes in the literature. In other words, if the intervention shows significant success or failure, the results get published; however, if the results are ambiguous, the study will not get published. This, of course, skews the bigger picture. And this isn't the only study questioning the trial literature. Here a just of few examples of very recent articles about such problems:

1. Here is a systematic review showing that trials are often stopped early if a significant benefit occurs.
2. Here is a very recent article in the Annals of Oncology reporting specific cases in oncology of ceasing trials for wanted results
3. An article in the Lancet questions why several completed trials have never been published
4. And finally in the NEJM an article about questionable outcome reporting.

So, in conclusion, it is always more effective and efficient to look for answers in the pre-appraised review literature; however, a search in the primary literature is often warranted because of the lack of currency of published reviews and simply because not all clinical questions have useable and available systematic reviews for an answer. But if you use single studies to answer a clinical question, some appraisal and corroboration is needed.

You have completed Module 4.