Searching the Medical Literature & Working with Sources

Introduction

To find the best – meaning the most relevant and valid (ie, "probably" true) – studies for appraisal, it is necessary to have an approach to searching the medical literature. The following tool provides a simple approach to get you started searching successfully. To make this simple, we are assuming that you are using **PubMed** (www.pubmed.gov) for primary sources of evidence (ie, original research studies).

Tip: You may wish to try various searches for your question. For example, if you want to know about publication bias, your first search may be "publication bias." After you have read a relevant article and scanned the references, you decide to do another search. This time you add the term, "grey literature." Because of the large number of hits, you limit the search to meta-analyses or systematic reviews.

For a detailed, interactive tutorial with animation and lots of "show me" information, we recommend the **PubMed Tutorial** on their homepage.

Note: Some of the resources listed here may be available only through payment or a subscription.

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Strategies & Steps

It is our suggestion that you start first with **Systematic Reviews**. If you are unable to find systematic reviews to serve as a basis for your topic, then see the appropriate sections for primary sources.

Steps for Working with Secondary Studies and Secondary Sources

Quality Issues

Quality of any source—even those with the best potential or reputation for quality—is **variable** Here are our most conservative suggestions for working with any source:

- The secondary study or source needs to be critically appraised using a tool appropriate for that purpose—PLUS the science used by the secondary study or source needs to be evaluated for validity and clinical usefulness.
- It is highly recommended that users review the methods used by the authors of the secondary study or source for critical appraisal considerations
- The most conservative approach is to review all studies considered to be of acceptable quality—and compare your outcomes to that of the review
- A less conservative approach is to audit a sampling of included studies

How to Audit a Secondary Source

- Of the included studies, critically appraise one or more original studies identified as high quality and one or two of the lowest quality
- If these pass, it is probably reasonable to assume that the rest of the studies are of sufficient validity and clinical usefulness
- A review that does not pass a critical appraisal review might still be usable as a foundation if the search strategy and criteria for excluded studies is sound.
 - If yes, critically appraise all studies selected for inclusion, discarding any not meeting a rigorous critical appraisal screen for validity and clinical usefulness.
 - Update using date of search and match study type to your question, critically appraising relevant studies.

Match Your Clinical Question to Study Design Type

Seek out original studies or systematic reviews of the study types below to appraise for validity and usefulness.

Question Topic	Study Design Features	Study Type
Treatment, Screening or Prevention – What happens when you do something to someone?	Experiment = Randomize appropriately and compare groups	RCT
Diagnosis – Does it do what it is supposed to do & does it improve care?	Need data to calculate sensitivity/specificity/predictive values – independent, blind comparison with a "gold standard"	RCT/ Cross-sectional
Natural history – What happens when you follow natural course of a condition?	Not an experiment – follows what actually happens over time	Cohort
Prognosis – What happens when you follow the natural course of a condition?	Not an experiment – follows what actually happens over time	Cohort

Answering a Clinical Question – Quick Steps

(For details, see specific sections in this document)

Strategy 1	1. Start with "best sources" e.g., Cochrane, DARE (more details are provided below) and Dynamed.	
"Best Sources"	 For Delfini to designate a source as "best" means that we generally agree with their methods and consider their outcomes to possibly be valid, however, even with best sources, there can sometimes be varying quality and we advise you to critically appraise the evidence for validity and usefulness. 	
	2. Information from best sources must be evaluated – or at least audited by appraising what they consider to be a "quality study"—and updated.	
	3. Ultimately, you may wish to synthesize your information (see Delfini Evidence Synthesis Tool)	
Strategy 2	If you cannot find information from a best source, you may wish to –	
PubMed	Search PubMed for a systematic review – you must appraise and update the review (updating includes appraising the new studies identified)	
	 Anything you obtain from PubMed, that is not from one of the "best sources", should be critically appraised for validity and for usefulness. 	
	2. Search PubMed for large studies (matching study type to your question) – you must appraise these	
	3. Search for a guideline or performance measure or other clinical recommendation – you must appraise and update these. See detailed instructions below.	
Time Saving Tips	PubMed provides easy links to comments and related articles. Someone may have addressed an important critical appraisal issue or something else of interest to you, so it might be fruitful to check out those links.	
	If you find a review, see if DARE has already critically appraised it.	

Searching Tips

Question Framing	For all searches, you must first frame a focused and specific clinical question to develop your search strategy and guide you through your subsequent work such as generating conclusions.
& Formulating	Example: You want to know: "Do patients with insulin-dependent diabetes have improved outcomes with improved glycemic control?"
a Search Strategy	From this focused question, create a one- or multi-part search question (ie, condition or condition plus intervention, exposure, characteristic or risk factor).
	Search: insulin-dependent diabetes glycemic control
	Adding descriptive words can help you narrow your search. You may find PICO and PICOTS useful for modifying searches which add population, comparator, outcomes, timing and setting. [Ref: Sackett et al and AHRQ]
	Examples: Adding terms like adult, children, acute, chronic, naming a specific drug, etc. (e.g., "acute bronchitis adults antibiotics)."
	Key Point : To be sure your search included MeSH terms (Medical Subject Headings) click on the

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"Details" button and look for "MeSH Terms." **Condition** is likely to give you a MeSH heading; **population** terminology is not.

For non-clinical topics and when your search doesn't trigger MeSH terms: You might need to use synonyms to capture what you are interested in: doctor patient relationship OR communication OR bedside manner OR rapport, etc. Review references of key articles for ideas.

Search Tips for PubMed

Order

You can input terms in natural language and in any order: postmenopausal hormone replacement cancer breast

About Boolean Operators

OR – Broadens (Apples OR oranges = gives you all entries with either term)

- use OR for "brand name OR generic" to get both
- No order needed = "antibiotic pediatric" same as "pediatric antibiotic"

AND - Narrows - each condition has to be met for results (automatic in PubMed)

Apples oranges = only entries with both terms

NOT - Excludes

- Best to keep it simple and do multiple searches rather than one huge comprehensive search
- Boolean operators -- AND, OR, NOT -- must be entered in uppercase letters
- Boolean operators are processed from left to right
- Use parentheses to nest terms together needed for multiple operators

Truncation

* operates as a wild card

Truncation turns off automatic term mapping and the automatic explosion of MeSH terms

Heart attack* will not map to the MeSH term *Myocardial Infarction* or include any of the more specific indentions, such as *Myocardial Stunning*

About Related Articles

If you find a relevant study in PubMed it is useful to click on the Related Articles button to retrieve similar studies

Advanced Skills

If you wish to go deeper for more complex searches (Boolean connections and search order; nesting, etc.), see the excellent information in the PubMed Tutorial. Frequently you will want to add Limits (e.g., study type, dates and other restrictions). We also recommend the use of My NCBI, an option that allows you to choose up to five filters for sorting your search results into categories (e.g., Clinical Trials RCTs, Systematic Reviews, Meta-analyses, Practice Guidelines). Clinical Queries (see below) is also useful when applying limits.

Searching for Harms

Searching for Harms

You may need to consider doing separate searches for harms. (See Delfini Tool for Evidence Grading, Wording Conclusions & Results Tables for Cautions Regarding Safety Findings Generally)

- Large RCTs should be sought, but harms might be rare or late. Look for long-term follow-up of RCTs. Many adverse effects, however, are too uncommon to be observed in RCTs. It is reasonable, therefore, to include lower quality evidence for harms
- Systematic reviews of RCTs should be sought, but harms may be described in various ways in different studies or not reported. It may be useful to cast a wide net with search terms such as "overview OR review OR systematic review OR meta-analysis" along with the search terms

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mentioned below.

- Search for case-control and cohort studies bearing in mind the threats to validity of observational studies
- Consider using the intervention in the search terms along with the following words: (harm OR harms OR adverse effect OR adverse effects OR adverse reaction OR adverse reactions OR adverse reaction monitoring OR ADR OR ADRS OR pharmacovigilance)
 - o Adapted from: BMJ. 2004;329:2-3; BMJ. 2004;329:44-47
- In addition, the Cochrane Handbook makes several useful suggestions:
 - Consider use of the search terms: (complications, side effect, toxic effect, toxicity, adverse event, safety, tolerability)
 - Searching for relevant synonyms (e.g., lethargy, tiredness, malaise)
 - Be prepared for several iterations in the searching
 - Be aware when using free text of differences in spelling, endings of words (e.g., singular and plural) Delfini note: consider using wild cards such as complication*
 - "No single approach can be relied on to yield all the studies effects of an intervention"
 - Judgment is required "to balance comprehensiveness (sensitivity) against precision"
 - Judgment is required when considering the use of additional sources such as regulatory agencies, reference books (e.g., on adverse effects), registries and other sources
 - Ref: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [updated September 2011]. http://handbook.cochrane.org/ (accessed 29th February 2016).
- Delfini frequently uses additional searches for harms. The number of additional searches depends on the project and requires judgment. For example, if the clinical question is, "What is the evidence for benefits and harms in arthroscopic debridement and lavage of the knee for osteoarthritis?," and the searcher wishes to know about the risks of deep vein thrombosis from all studies where arthroscopy is the intervention in osteoarthritis of the knee, one might chose to do an additional search in PubMed for arthroscopy without the terms "debridement, lavage" but with the search terms, "osteoarthritis knee arthroscopy deep vein thrombosis" in order to identify studies reporting DVT complications in arthroscopy. Other additional searches could be performed.

Also, you may wish to use the **US Food and Drug Administration (FDA) Website**. The site is huge and complex to navigate. It requires patience and persistence to find relevant information. However, for those interested in detailed information from the FDA for drugs or medical devices, the search function on the home page and the search functions on the drug and medical device pages can provide—at times—useful information. See standard **CAUTION** on our website about the variable quality of this information. http://www.fda.gov

Searching with Symbols

- Search: beta blockers heart failure yields ~9,000 hits
 - QUERY TRANSLATION: ("BETA"[Journal] OR "beta"[All Fields]) AND blockers[All Fields] AND
 ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart
 failure"[All Fields])
- Search: β-blockers OR beta-blockers heart failure yields ~94,000 hits
 - QUERY TRANSLATION: ("adrenergic beta-antagonists"[Pharmacological Action] OR "adrenergic beta-antagonists" [MeSH Terms] OR ("adrenergic" [All Fields] AND "beta-antagonists" [All Fields]) OR "adrenergic beta-antagonists" [All Fields] OR ("beta" [All Fields] AND "blockers" [All Fields]) OR "beta blockers" [All Fields]) OR (("adrenergic beta-antagonists" [Pharmacological Action] OR "adrenergic beta-antagonists" [MeSH Terms] OR ("adrenergic" [All Fields] AND "beta-antagonists" [All Fields]) OR "adrenergic beta-antagonists" [All Fields] OR ("beta" [All Fields]) OR "beta blockers" [All Fields]) AND ("heart failure" [MeSH Terms]) OR ("heart" [All Fields]) AND "failure" [All Fields]))

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Systematic Reviews for All Study Types

IMPORTANT Update & Evaluate	After you find a systematic review you wish to use, you MUST search for valid and useful studies that may have been published after the time period captured by the systematic review. • You need to appraise these for validity. • For valid studies, you need to assess the usability of the results. For questions of therapy, prevention and screening (and potentially diagnostic testing) – look for SRs limited to the inclusion of RCTs.	
IMPORTANT RCTs		
Best options for systematic reviews > You should evaluate the evidence for validity and usability Update and appraise new studies.	Start with these resources (some of which may be through subscription only): The Cochrane Collection www.cochrane.org Cochrane focuses on the effects of health care interventions. (Includes DARE below.) Database of Abstracts of Reviews of Effects (DARE) http://www.crd.york.ac.uk/CRDWeb/ DARE identifies potential systematic reviews and assesses them for methodological quality against a set of inclusion criteria and summarizes the results. TIP: If DARE finds significant problems with a review, be forewarned that their language is subtle. If they state, "Use with caution," the review should probably not be used to address questions of efficacy DynaMed http://www.dynamed.com/home/	
Using PubMed for meta-analyses →	 Go to PubMed (<u>www.pubmed.gov</u>). Sign up for or sign into My NCBI. Go to Advanced search. 	
You must critically appraise these studies and assess the results for usability	 Enter your one- or multi-part search question. See PubMed Search Tips in the Searching Tips Box on page 2. If you get more than several pages of hits and you want fewer, scroll down to Type of Articles and limit to Meta-Analysis or scroll down further to Subsets and check the box for Systematic Reviews 	

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Primary and Secondary Sources (i.e., Original Research Articles and Summaries of Original Research)

This tool focuses on finding primary studies through **PubMed**. There are some other sources you may wish to use as well. For example, two of our favored sources are the ACP Journal Club (ACPJC) and Dynamed. Content is carefully selected from over 100 clinical journals through reliable application of explicit criteria for scientific validity. ACPJC summarizes important studies and then comments on the validity or relevance to medical practice. Be aware that the specialist writing the commentary may have biases. Dynamed organizes reviews by clinical condition, so you can review what Dynamed considers to be the important studies on a topic. You need to decide upon using best sources that critically appraise information for you or you need to critically appraise articles yourself.

For Studies Dealing with Treatment or Prevention

If you are looking for studies dealing with treatment or prevention , follow these steps \rightarrow
You must critically appraise these studies and assess the
results for usability.

- 1. Go to the **PubMed** (www.pubmed.gov)
- 2. Enter your one- or multi-part search question. See **PubMed** Searching Tips above.
- 3. If you get more than several pages of hits and you want fewer, click the limits button and limit to **Meta-Analysis**
- 4. If you still have more than several pages of hits, try being more specific with your question.
- 5. To limit your search to a specific study type look at the left margin of PubMed and you will see **Article Types**. If you want to limit your search to RCTs (or any other study design), click on "Customize..." A drop down box will appear with many options. Check the box for **Randomized Clinical Trial** or **Clinical Trial** and then at the bottom of the box click **Show**. You will then be returned to the search screen and you can select the study type you have added to the search page. We suggest using the **Clinical Trial** option rather than—or in addition to—the **Randomized Clinical Trial** option because the **Randomized Clinical Trial** filter at times misses important randomized controlled trials picked up by the more sensitive **Clinical Trial** filter.

A second way to find **studies** dealing with **treatment** or **prevention** → You must **critically appraise** these studies and **assess the results** for usability

- Before beginning your search scroll to the bottom to **PubMed Tools** and select **Clinical Queries**
 - a. Click **Therapy**.
 - b. Enter your search terms.
 - c. You will now see a dropdown window and you can click <u>Broad</u> which will get you a greater number of hits, but with more irrelevant articles, or you can click <u>Narrow</u> which will get you fewer hits and more relevant articles, but you may miss some useful articles.

If you are looking for information about a **specific drug**, (e.g., a drug recently approved by the **FDA**) you may wish to follow these

- Go to www.fda.gov
- On the left you will see **Drugs** which has a pulldown window
- Your goal is to find Medical Review(s) for the drug of interest
- On the pulldown menu labeled Drugs Select Drug Information (Drugs@FDA)

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steps →	(Under Spotlight on the right side of the page)
	Search for drug or obtain from index
	Select Approval History, Letters, Reviews, and Related Document
	Select Review
	Select Medical Review (NOTE: you won't see the Medical Review listed until several months after approval)
	Read Efficacy/Safety sections and other sections of interest in the Medical Review
	Google searching may be useful and faster. Example: "etanercept FDA" 1. Etanercept Product Approval Information – Licensing Action 12/2/98
	Approval Letter (PDF)
	• Label (PDF)
	SBA (PDF)
	Review Documents Clinical Pharmacokinetics Review (PDF) Clinical Review (October 28, 1998) (PDF) Clinical Review (December 1, 1998) (PDF) CMC Review (PDF) Nonclinical Pharmacology and Toxicology Review (PDF) Statistical Review (PDF)
	2. enbrel medication guide - Food and Drug Administration [Information for patients]
If you are looking for FDA information dealing with medical devices , you may also wish to follow these steps \rightarrow	 Go to http://www.fda.gov On the left, click pulldown menu Medical Devices and then Approvals and Clearances on the right side of the page and then Recently-Approved Devices Select the device of interest Scroll almost to the bottom and you can go the PDF with efficacy and safety studies by clicking on Additional information: Summary of Safety and Effectiveness and labeling are available online.

	Effectiveness and labeling are available online.
For Studies Dealing with	Diagnosis, Etiology or Prognosis
f you are looking for studies	1. Go to the PubMed (<u>www.pubmed.gov</u>)
dealing with diagnosis, etiology or prognosis, the	2. Scroll to the bottom and select <u>Clinical Queries</u> under <u>PubMed Tools.</u>
easiest way to search	3. Enter search terms
PubMed is to use the <u>Clinical</u> Queries filter.	4. Click pulldown <u>Category</u> as applicable (e.g., diagnosis, etiology or prognosis).
Follow these steps -> You must critically appraise	5. You can click in the pulldown window Broad which will get you a greater number of hits, but with more irrelevant articles, or you can click Narrow which will get you fewer hits and more relevant articles, but you may miss some useful articles.
these studies and assess the results for usability.	 Enter your one- or multi-part search question. See Using PubMed on the lef side of the page for more information.
	 In the left hand column you see the Clinical Queries results and to the right of that the Meta-analysis results.

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8. If you still do not get what you want, look for cross-sectional studies with gold standard for diagnosis, and look for cohort studies for etiology and prognosis.

Example: In the **Clinical Queries** window click the **Diagnosis** button and type in "**prostate cancer PSA.**" This will retrieve a large number of hits. To narrow it down select advanced search and scroll down to **Types of Articles** and select **Meta-Analysis.** This will retrieve a very small number of hits.

For Clinical Practice Guidelines and Other Clinical Content

There are numerous webbased sources where you can find "seed" guidelines.

Our favorite sites are here →

You need to critically appraise these.

You will need to -

- ➤ Update the evidence for almost all guidelines you use (look at the date of the search strategy or most recent dated reference); appraise for validity & assess for results usability.
- ➤ Project the impacts of practice change in health outcomes, patient and clinician satisfaction, costs or savings and other considerations (triangulations).
- Create information and decision tools for your clinicians and

We favor the following sites because they attempt to -

- 1. Provide a comprehensive list of guidelines, or
- 2. Provide guidelines based on the best available evidence as determined by a systematic search and review of the medical literature
 - National Guideline Clearinghouse www.guideline.gov

This site is comprehensive, but "user-beware" — the guidelines vary in method of development. Some are based on consensus, some are evidence-based and for some, the process of development is unknown to the reader.

This site contains a feature that allows you to simultaneously compare two or more guidelines for the details of development of the guidelines you choose. This is of great value in evaluating guidelines. Choose the **Compare Guidelines** feature.

New Zealand Guidelines Group

http://www.nzgg.org.nz/index.cfm?screensize=1024&ScreenResSet=yes

The process of development is well-documented for each guideline.

US Preventive Services Task Force (USPSTF)
 http://www.uspreventiveservicestaskforce.org/BrowseRec/Index

An independent panel of primary care systematically reviews the evidence of effectiveness and develops recommendations for clinical preventive services.

PubMed (Medline) www.pubmed.gov

- 1. Enter search terms, e.g., "prostate cancer."
- 2. On the left find "Article types."
- 3. Select "Customize."
- 4. Scroll down and select "Guideline" and at the bottom select "Show."
- 5. The search screen returns; now select guideline (you will see a a checkmark appear").
- 6. The search will then be carried out.

Searching the Medical Literature & Working with Sources patients.

Delfini Evidence Tool Kit

For Content Developers: Guidance

Doc	Document your search strategy below.		
#	Category	Fictional Examples/Guidance as Applicable	
1.	Date of Search	 Notes: Include the date of your search and any dates of updates to your search. When selecting systematic reviews, record the date of the search for the systematic review in addition to any record of the publication date. 	
2.	Search Question(s)	Example: Which interventions are of clinical benefit to patients with chronic kidney disease?	
3.	Sources Searched	Example: Cochrane DARE PubMed	
4.	Criteria for Review of Study	Example: For efficacy, effectiveness we included valid and useful systematic reviews and meta-analyses, and randomized controlled trials dealing with clinically meaningful health and health care outcomes. For adverse events we also included observational studies, information from the FDA website. We excluded observational studies dealing with therapy, prevention or screening, editorials, opinion pieces, narrative reviews, animal studies, studies with clinically non-useful outcomes, open-label studies, subgroup analyses, non-relevant studies (e.g., intermediate markers not causally proven to affect meaningful patient outcomes in the areas of quality of life, mortality, morbidity, functioning, symptom relief). The guideline team made a decision to rely upon evidence from the following guidelines and other sources without critically appraising the original sources for validity: K/DOQI Guideline—Search dates through July 2002, references added by experts after 2002. References included are through 2003. CMI guidelines Cochrane Collaboration Clinical Evidence DARE	
5.	Criteria for Inclusion	 Example: We included only evidence with evidence grade of B or above (see table of excluded studies with rationale for exclusion) and evidence from the following sources: K/DOQI Guideline—Search dates through July 2002, references added by experts after 2002. References included are through 2003. CMI guidelines Cochrane Collaboration Clinical Evidence 	

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		■ DARE
6.	Search Strategy and Results for Dare, Cochrane, and Clinical Evidence (include search dates for Clinical Evidence and Cochrane)	 Example: Search terms: "Chronic kidney disease" DARE: Search date: 5/17/05. Search terms: Chronic kidney disease 24 hits—saved 10 after excluding non-relevant reviews Cochrane Systematic Reviews: Search date: 5/20/05 Search terms: Chronic kidney disease 187 hits—saved 6 after excluding non-relevant reviews Cochrane Central Register of Controlled Trials. Search date May 30, 2005: Search terms: Chronic Kidney Disease. 58 hits No additional studies were added from Cochrane Central Register as all hits were duplicates. Clinical Evidence: Search date: 5/17/05: Search terms: Chronic Kidney Disease—6 relevant hits reviewing hypertension primary prevention, diabetes nephropathy, prevention secondary complications in CKD, prevention acute renal failure in high risk patients.
7.	Search Strategy and Results for PubMed Primary Studies	 Example: Search date: May 20, 2005 Search terms: prevention chronic kidney disease/chronic kidney disease with RCT limits—from 2003 through 5/20/2005 PubMed Translation: (chronic[All Fields] AND (("kidney diseases"[TIAB] NOT Medline[SB]) OR "kidney diseases"[MeSH Terms] OR kidney disease[Text Word]) AND ("prevention and control"[Subheading] OR prevention[Text Word])) AND Randomized Controlled Trial [ptyp] Yield: 1398 hits; the team reviewed only citations 2004-2005 since 2003 studies were reviewed by K/DOQI 74 relevant studies were selected for further review.
8.	Search Strategy and Results for PubMed Systematic Reviews Using Clinical Queries	 Example: Search Date: May 18, 2005 Search Engine Used: PubMed Clinical Queries → Systematic Reviews Search terms: chronic kidney disease prevention PubMed Translation: (Chronic[All Fields] AND (("kidney diseases"[TIAB] NOT Medline[SB]) OR "kidney diseases" [MeSH Terms] OR kidney disease[Text Word]) AND ("prevention and control" [Subheading] OR prevention [Text Word])) AND systematic[sb] Yield: 97 hits—39 relevant hits published after 2003 (most recent references from KDOQI) were selected for further review
9.	Evidence Synthesis and Clinical Recommendations	Example: Relevant studies were distributed to team members for critical appraisal and evidence grading (see below for grading scale). Dyads of team members reviewed the selected studies with an experienced literature reviewer participating in each dyad. Each group summarized their work in Delfini templates and presented/discussed their reviews at an in-person team meeting in October 26, 2005. Evidence synthesis tags are the same as those used for evidence grading of individual studies (see chart below). The following tags were applied to clinical recommendations: Clinical Recommendation Tags: Grade A Recommendation: Useful Evidence – Appears sufficient to use in

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		 making health care decisions. Grade B Recommendation: Possibly Useful Evidence— Might be sufficient to use in making health care decisions. Grade U Recommendation Based on Clinical Judgment of Experts (Lack of Useful Evidence)
10.	Evidence Grading	Example: The Delfini Tool for Evidence Grading, Wording Conclusions & Results Tables was used to grade all relevant studies published after the search dates of the trusted sources. Details of the grading scale are presented in the Delfini Evidence Grading Tool.
		NOTE: For actual projects, you would want to detail the elements of the scale in your documentation. The details from the Delfini Tool are not being included here for reasons of economy.