# Process steps and suggestions for creating drug monographs and drug class reviews in an evidence-based formulary system: Update 07/09/2008

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**Abstract**

Given the high estimates of inappropriate healthcare decisions in this country and the well-documented evidence of inappropriate variations in healthcare, a well-functioning formulary system is of great importance. Bias in research tends to inflate or falsely report benefit in clinical trials of interventions by up to a relative 40% to 50%. Therefore, to ensure the adoption of products with valid and clinically useful outcomes, formulary systems should include in their processes the key steps used in evidence-based medicine, including the evaluation of therapeutic studies for bias and clinical usefulness to inform formulary decisions. This article outlines requirements and suggestions for obtaining studies with appropriate designs and acceptable methodology and execution, and emphasizes why such studies should be the basis for developing drug monographs and class reviews and informing decisions. (*Formulary*. 2008;43:135–145.)

Historically, many physicians have objected to formularies because of the perception that formularies limit prescribing choices. However, it is estimated that 20% to 50% of all healthcare decisions in the United States are inappropriate.[1–4] Therefore, it is reasonable to conclude that an evidence-based formulary is an important tool that provides users with high-quality information to aid decision making and ensure the inclusion of only agents that have been demonstrated via research that is valid (ie, probably true) to be clinically useful.[5] This paper discusses the importance of an evidence-based formulary process and outlines the steps required for creating high-quality, evidence-based drug monographs and drug class reviews.

## WHY AN EVIDENCE-BASED FORMULARY SYSTEM?

Clinical judgments should be informed, when possible, by valid and clinically useful evidence that is likely to result in improved outcomes in the areas of morbidity, mortality, symptom relief, physical or emotional functioning, and/or health-related quality of life. Unfortunately, many physicians, clinical pharmacists, nurses, and other healthcare professionals, along with many of those providing information to these practitioners, such as pharmaceutical manufacturers, researchers, editors, peer reviewers, publishers, and other medical information content providers, lack the skills necessary to adequately differentiate high-quality studies from poor ones; this fact has been strongly supported by our direct experience working with numerous groups nationwide.[6,7] The problem of poor research and critical appraisal skills is compounded by the weekly publication of thousands of flawed and misleading studies and opinions, even in the best medical journals. Each week, approximately 12,000 articles are added to the National Library of Medicine. It is our estimate, having evaluated thousands of published studies, that approximately ≤10% of published studies in the healthcare literature are both valid and clinically useful; others have estimated that this number is <5%.[8] In discussions concerning the state of scientific knowledge, the Institute of Medicine concluded that it was plausible that only 4% of interventions used in healthcare have strong evidence to support them.[9]

Critical appraisal matters. In a classic study, Chalmers et al[10] demonstrated that a lack of concealment of allocation inflated the appearance of benefit, as did a lack of randomization, in studies with an outcome of fatality from acute myocardial infarction (MI). Studies that were randomized with concealment of the allocation sequence, on average, reported nonsignificant findings. As studies diminished in quality in these 2 dimensions, benefit was inflated as high as an absolute 10% in favor of the intervention. This translates into a number-needed-to-treat (NNT) of 10, which would be highly clinically significant if only it were true. Results of subsequently published studies have supported the conclusion that bias tends to favor the intervention, inflating benefits by up to a relative 40% to 50%.[11–15] These high rates of falsely inflated results have been demonstrated in studies in which methods such as generation of the randomization sequence, concealment of allocation, blinding, and assessing outcomes through statistical modeling are omitted or not done correctly.[11–15]

Although FDA is charged with ensuring the safety and efficacy of drugs and biologic products, the agency cannot be relied on as medical decision-makers' sole source of information about the safety and efficacy of drugs. Skilled formulary groups can help solve this quality information deficit by conducting rigorous critical appraisals of the medical literature for validity and usefulness for all agents being considered for formulary inclusion. An evidence-based approach to the evaluation of drugs

is the only reliable way to know if the drug being evaluated is likely to be responsible for the reported outcomes in a study (ie, the study is valid) or if the results are likely due to bias, confounding, or chance (ie, the study is invalid). A good formulary system continuously evaluates new evidence, incorporates valid and useful information, and monitors drug usage. Such monitoring, coupled with considerations of value, is the hallmark of a high-quality formulary system.

The first key to an evidence-based formulary system, therefore, is to ensure an understanding of the relevant science. Groups can then consider other factors, such as clinical attributes; community standards; risk management considerations; patient, clinician, and employer satisfaction; cost; marketing implications; utilization; and other factors when making formulary decisions.

## BUILDING A DRUG MONOGRAPH OR DRUG CLASS REVIEW

There are 5 general steps for building a drug monograph or drug class review. These steps, which are outlined in Table 1, include compiling background information, identifying potentially useful scientific evidence, critically appraising that evidence for validity and evaluating results, summarizing the evidence, and creating an overall summary for the monograph or class review and making recommendations.

**Background information.** Drug monographs and drug class reviews are the foundation of high-quality formulary systems. These summaries of a drug's efficacy, advantages and disadvantages, FDA status, and other information are a central component of the pharmacy & therapeutics (P&T) process. If monographs and class reviews are created using a rigorous evidence-based process, they can be used by decision-makers as trusted resources for guiding clinical care decisions, weighing alternatives, and evaluating claims made about drugs and users' opinions or judgments. Once it has been determined that an agent will be considered for formulary inclusion, the monograph or class review should be created to contain information about the current national and local standards (eg, treatment guidelines, national and local expert opinions); labeling information, including FDA-approved indications, pharmacology, warnings/precautions, adverse events (including abuse and dependency issues), etc; interactions; therapeutic equivalents; and other therapeutic alternatives. Table 2 contains a list of resources that can provide much of this background information

**Table 1**
**5 Steps for building a drug monograph or drug class review**

| Step | Description | Key Points |
|---|---|---|
| 1 | Compile background information | • Sources (see Table 2), national guidelines, and informed expert opinion |
| 2 | Identify potentially useful scientific evidence | • Focused clinical question (include condition and intervention)<br>• Documentation of search strategy including sources, terms, and limits; dates of searches; search yield; and number of relevant studies selected for further review<br>• Audit all secondary studies and sources used |
| 3 | Critically appraise the evidence and evaluate the results | • Evaluate for efficacy and safety<br>• Look for lethal threats to validity (see Table 3)<br>• Critically appraise (see Table 4)<br>• Summarize key threats to validity<br>• Assign an evidence grade (see Table 5) |
| 4 | Summarize the evidence | • Narrative statement that includes the quality of the evidence and the strength of the conclusions and/or recommendations<br>• Include information regarding the number of studies, number of subjects, population characteristics, and homogeneity or heterogeneity of the included studies, etc.<br>• Limitations of the evidence review<br>• Evidence summary grade |
| 5 | Create an overall summary | • "Roll-up" of previous steps (see Table 6)<br>• Clearly distinguish evidence from recommendations<br>• Address findings regarding efficacy and safety, appropriate patient population, important clinical considerations, value assessment, comparison to alternatives, implications for practice change, and recommendations, etc.<br>• Additional considerations include the patient perspective (eg, benefits, costs, risks, harms, uncertainties, and alternatives, satisfaction) and issues that may affect treatment adherence, and potential problems with issues such as drug dependency or the potential for abuse. The clinician's perspective is also important and includes satisfaction, acceptability and actionability.<br>• Describe limitations |

Adapted from the Delfini Intervention Review Template.

and conclusions from other "most trusted" secondary sources, such as groups performing high-quality systematic reviews.

**Table 2**
**Selected secondary sources for background information on drugs[a]**

Although many of the following sources can be relied upon for background information, they should not be used for drawing conclusions about efficacy without deeper scrutiny, because the information presented may not be based on valid research studies. We strongly recommend that any secondary sources be audited to determine if the individual studies, upon which the conclusions are based, are in fact valid and clinically useful.

- Useful background information may be found on FDA website. The sections of the website that are especially useful include Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm) and the Center for Drug and Evaluation and Research (CDER) (http://www.fda.gov/cder/drug/default.htm). CDER is an up-to-date source for new drug applications (NDAs) and useful background information on new drugs. The FDA medical reviews and statistician reviews can be of great value. It is worthwhile to search using the agent's generic and proprietary name.
- The Health Technology Assessment (HTA) program, available from the British National Institute of Health Research (NIHR) (http://www.hta.ac.uk/) provides healthcare technology and drug information. The purpose of the HTA program is to ensure that high-quality research is available on the effectiveness and cost of health technologies. HTA awards funding for monographs that are produced by groups who qualify for grant funding.
- The Canadian Agency for Drugs and Technologies in Health (CADTH) (http://www.cadth.ca/index.php/en/hta/reports-publications) provides evidence-based information on drugs and healthcare technologies.
- The following websites may be of value for information on clinical background and available alternatives, and often provide efficacy and safety reviews:
  - The Cochrane Collaboration (http://www.cochrane.org/index.htm)
  - DynaMed (http://www.ebscohost.com/dynamed)
  - Turning Research Into Practice (TRIP) database (http://www.tripdatabase.com/index.html)
  - Agency for Healthcare Research and Quality (AHRQ) (http://www.ahrq.gov)
  - *British Medical Journal* (*BMJ*) Clinical Evidence (http://clinicalevidence.bmj.com/ceweb/index.jsp)
- At times, the introductory paragraph of randomized controlled trials provides helpful background information.

[a] Several of these sources are available by subscription only. (As of this writing, free access to *BMJ* Clinical Evidence may be obtained through the United Health Foundation).

**Identifying potentially useful evidence.** The next step is to create a focused clinical question and then attempt to identify potentially useful scientific evidence. An efficient way to find high-quality information is to start with the most potentially reliable secondary sources, such as those listed in Table 2, to obtain systematic reviews. In addition to these sources, the Database of Abstracts of Reviews of Effects (DARE) (www.york.ac.uk/inst/crd/crddatabases.htm) can be helpful in identifying useful systematic reviews. DARE, which is maintained by University of York, identifies potential systematic reviews, assesses them for methodological quality against a set of inclusion criteria, and summarizes the results.

At the time of publication, we are unaware of any secondary source that is fully reliable. Therefore, critical appraisal auditing must be done for each systematic review being considered for inclusion in the drug monograph or class review. When auditing a secondary source, select ≥1 studies determined by the secondary source to be of the highest quality and see if they pass the appraisal. If so, select ≥1 studies determined to be of the lowest quality and see if they pass the appraisal. If both the higher- and lower-quality studies pass appraisal, it is reasonable to conclude that only quality primary sources were used in the secondary source.

If a secondary source from the originally selected sources cannot be used, the National Library of Medicine, accessed through PubMed (www.pubmed.gov), can be useful to find other systematic reviews, including meta-analyses or randomized controlled trials (RCTs). The type of article to search for can be specified using the "Type of Article" variable (found under the "Limits" section). It is advisable to use the agent's generic and proprietary name when searching PubMed. It is necessary to critically appraise all studies obtained from a PubMed search. Systematic reviews obtained from PubMed can be crosschecked by determining whether DARE has already evaluated the reviews. Editorials, comments, and related articles can provide additional information to aid in the critical appraisal process.

If any secondary source does not pass a critical appraisal audit, a source might still be usable as a basis for a monograph or class review if it is agreed that the search and exclusions have been performed rigorously. In this instance, the conclusions of the review would not be used, but rather all studies selected for inclusion in the review should be critically appraised; any that are deemed to not be

both valid and clinically useful should be discarded. In this case, it is necessary to update the review with subsequent research published after the date of the secondary study's search.

Information from any secondary sources almost always requires updating, which entails a search for any studies published after the search date of the systematic review and critical appraisal of the studies determined to be potentially valid and relevant. To update, it is important to use the same search date that was used by the secondary source, rather than the publication date, which may be much later than the search date.

When documenting your search, it is helpful to include information about the clinical question or focus point of the search, sources, date of search, search terms, limits used, number of hits, number of irrelevant studies (documented with citation), and number of studies selected for review (documented with citation). Documenting the PubMed Identification Number (PMID number) and using it as a search variable is an efficient way to relocate studies.

**Critical appraisal for validity and assessment of results.** There are many textbooks available on the topics of clinical epidemiology and critical appraisal techniques.[16–18] It may be helpful before starting a drug monograph to outline selected key components of an ideal study and use this model to compare the available studies. It is useful for this model study to contain a rough benchmark for outcomes, study length for the outcome of interest, measurement methods, population, dosing, comparators, potency equivalents, and washout length. Studies must be assessed for relevance to the clinical question and for lethal threats to validity or clinical usability, which would exclude the study from further consideration. Transparency is an important hallmark of evidence-based clinical decision-making, and so it is recommended to document the study reference and the reason(s) for excluding the study. Table 3 details some of the common lethal threats that can be quickly identified, any of which may be sufficient to exclude a study from consideration. Table 4 provides an additional checklist to further identify potential reasons for study exclusion. The goal of these assessments is to summarize threats to validity so that an appropriate grade of evidence can be assigned. Explicit details must be provided by the author, or a threat should be assumed (eg, if a paper reports that patients were randomized, but does not include details providing assurance of quality randomization methods, a threat should be

**Table 3**
**Initial checklist to help identify lethal flaws in published clinical trials of therapeutic interventions appropriately documented.**

This checklist can help to quickly identify lethal flaws within a study. The trial could be considered invalid if any of the following exist:

1. Issues with study type
    a. Observational studies for efficacy of therapy, prevention, or screening interventions, unless the results are all-or-none results (standards are lowered for study quality when evaluating safety issues, but our advice is to take a net view and ensure that the wording of the conclusions is not misleading and that the strength of the evidence is described as being weak if that is the case)
    b. Case series (including reports using comparisons with historical controls or "natural statistics") unless the results are presented as all-or-none, which is extremely rare
2. Methods that increase chance findings
    a. Use of post hoc analyses (ie, using study outcomes or research questions that are not determined in advance) to draw conclusions regarding cause and effect
    b. Subgroup analyses in which the subgroups are not determined in advance
3. Lack of meaningful clinical benefit or other issues with outcomes
    a. For clinical questions, a lack of clinical significance (end points need to address direct and meaningful benefit with regard to morbidity, mortality, symptom relief, emotional or physical functioning, and/or health-related quality of life, or there needs to be other valid evidence that demonstrates a causal link between the study outcomes and a clinically significant outcome)
    b. Effect size is not clinically meaningful
    c. Nonsignificant findings are reported, but the confidence intervals include clinically meaningful differences, which would result in a lethally threatened conclusion
    d. For noninferiority and equivalence trials
        1. Lack of sufficient evidence confirming efficacy of referent treatment
        2. Inappropriate deltas (inferiority should be set at the smallest meaningful clinical benefit, equivalence should be set narrowly)
        3. Significant biases or analysis methods that would tend to diminish an effect size (conservative application of intent-to-treat analysis, which would tend to diminish differences between groups resulting in a bias towards equivalence or noninferiority, insufficient power, etc)

Adapted from the Delfini Intervention Review Template.

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**Table 4: Secondary checklist to help identify selected flaws within clinical trials of therapeutic interventions**

This checklist can help to quickly identify selected flaws within a study. Consider the following when assessing the validity of trial results that were not deemed to be invalid using the initial validity checklist::

1. Was the study design appropriate to assess the research question? Was the research question useful?
2. If composite endpoints were used, were they reasonable? And if composite efficacy endpoints were used, were reasonable composite safety endpoints also used?
3. Could bias, confounders (known or unknown), or chance explain the study results?
4. Were the research questions, study population, outcomes, group assignment methods, study conduct methods, analysis methods, and measure of statistical significance prespecified and appropriate?
5. Were the groups included in the study appropriate, of appropriate size, concurrent, and similar in prognostic factors?
6. Were the methods for generating the group assignment sequence truly random? Did the sequencing avoid potential for anyone to affect the assignment to a study arm? Did the randomization remain intact throughout the study?
7. Were the allocation strategies concealed to prevent anyone from affecting assignment to a study arm?
8. Was the double-blinding adequately preserved throughout the study for the patients and all who worked with the patients or patients' data?
9. Were reasonable interventions and reasonable comparator(s) used?
10. Was the study free of bias or differences between the groups (except the topic being studied, eg, active agent vs placebo)? Considerations include intervention design and execution, co-interventions, concomitant medication use, adherence, inappropriate exposure or migration, crossover threats, protocol deviations, measurement methods, study duration, etc
11. Were any missing data points or loss from randomization minimal or nonexistent, except in cases where an appropriate intention-to-treat analysis or other reasonable sensitivity analysis has been performed[a] (eg, a loss of approximately 5% of outcome data with a differential loss between the study groups, or approximately 10% without a differential loss)?
12. Were the research assessors blinded?
13. Was there a low likelihood that results were due to chance or that nonsignificant results were due to an insufficient number of study participants? This analysis requires a judgment call on statistical and clinical significance, including a review of the confidence intervals to determine whether the boundaries are outside of what you consider to be clinically significant. If the results are outside those boundaries, the findings should be considered inconclusive.
14. Did any use of modeling include only reasonable assumptions?

a The phrase "intention-to-treat" (ITT) is often used by authors who have not actually performed an ITT analysis or who have performed it incorrectly. Evaluate whether outcomes are provided for all patients in the groups to which they were randomized and evaluate the method the researchers used to assign outcomes for missing values. You may be able to perform an ITT analysis by assigning outcomes for missing values that put the intervention or element of interest through a rigorous test. For example, you could test the *P* values by performing a worst-case scenario (also known as extreme case analysis). To do so, assign positive outcomes to missing controls and negative outcomes to missing study patients. If the results remain statistically significant and the other methodological considerations are acceptable, the study can be considered to have passed the worst-case analysis audit.

Adapted from the Evidence Grading Tool.


assumed). If sufficient flaws are identified to render a study invalid, the critique may be considered complete at that point, generally without a need for identifying further threats, and should be appropriately documented.

The critical appraisal should be documented by preparing a review that includes a summary of key study elements and the threats to validity, followed by an evidence grade. It is recommended that the evidence for both efficacy and safety be summarized.

Grading systems can vary significantly. Therefore, it is recommended that the specific criteria for each grade be reviewed, as definitions may vary among systems and some systems have flawed criteria that can upgrade low-quality or fatally flawed studies. When choosing a grading system from the many that are available, consider the ease of application, validity of the criteria, and ease of recollection. We use a system that combines these attributes with versatility so that the system can be used to grade studies, conclusions, or evidence syntheses for validity and clinical usefulness (Table 5).

**Table 5**
**Delfini Evidence Grading Scale**

Grade A evidence: Useful
- The evidence is strong and appears sufficient to use in making healthcare decisions. It is both valid and useful (meets standards for clinical significance, sufficient magnitude of effect size, physician and patient acceptability, etc)

Grade B evidence: Probably useful
- The evidence appears potentially strong and is probably sufficient to use in making healthcare decisions, although some threats to validity were identified

Grade B-U evidence: Possible-to-uncertain usefulness
- The evidence might be sufficient to use in making healthcare decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B status and the uncertainty is not great enough to fully warrant a Grade U. Therefore, sufficient threats to validity place the study into a "borderline" category

Grade U evidence: Uncertain usefulness
- There is sufficient uncertainty to warrant caution regarding the use of this evidence in making healthcare decisions

Adapted from the Delfini Evidence Grading Tool.


Evaluating safety data is a complex process. Adverse events often occur infrequently and are usually not prespecified as outcome measures in RCTs. Also, they may be detected long after completion of RCTs through observational reports. It may be reasonable at times to use safety data from lower-quality RCTs, because safety information from selected lower-grade RCTs may have greater

validity and usefulness than observational studies or case reports generated after RCTs are completed. However, it may be necessary to incorporate observational information into safety information if potentially significant risks are detected following the publication of an RCT. FDA postmarketing safety data may also be useful. As with efficacy data, safety data should be graded for quality and assigned an evidence grade. When safety outcomes are not prespecified, it can be useful to look for patterns across multiple studies to decrease the likelihood of drawing conclusions based on chance effects.

Conclusions about risks should be worded carefully so that information drawn from potentially flawed data regarding risks is not presented as if it is based on stronger research than actually exists. Although a study may be considered low quality overall, it may be sufficiently valid in one area, such as safety; therefore, it may be worthwhile to grade individual study conclusions rather than to assign a grade to the overall study.

**Summary of the evidence.** The goal of evidence synthesis is to summarize the best available valid and useful evidence into a conclusion. The evidence summary, or synthesis, is usually a text statement that includes both the quality of the evidence and the strength of the conclusion or recommendation. Language that is inaccurate, misleading, or vague, such as "Recent evidence suggests..." or "There is evidence that..." should be avoided. It is recommended that the statement include any limitations of the drug review and subsequent synthesis. And, just as it is recommended that a grade be applied to individual studies reviewed, so too should a grade be applied to the summary of the evidence.

It is also useful to include in the evidence synthesis some aggregated information about the studies used to create the monograph or class review, such as the number of included studies, number of patients, population characteristics, homogeneity/heterogeneity of studies included, etc.

**Summarize the review and make recommendations.** The final step in conducting the drug review is to create a concluding summary. This summary should be the "roll-up" for all of the preceding information that has been reviewed and synthesized. The summary should be very clear and transparent in distinguishing between evidence and conclusions or judgments. It should address issues such as efficacy and safety results, appropriate patient population, important clinical considerations, value assessment, comparison with therapeutic alternatives, implications for practice change, and recommendations. The summary should also describe limitations of the overall review and analysis. Table 6 contains some key characteristics that should be contained in a concluding statement. Additional inclusions should address the patient's concerns (eg, benefits, costs, risks, uncertainties, alternatives, and satisfaction), issues that may affect treatment adherence, and potential problems such as drug dependency or the potential for abuse. The clinician's perspective is also important and includes satisfaction, acceptability, and actionability.

It is advisable to consult with clinicians and others before writing the summary to gain their perspective on these considerations and also, specifically, to add committee considerations (including guidance, restrictions, and exclusions, giving consideration to substitutions, prior authorizations, and overrides).

## CONCLUSION

A well-written drug monograph or class review, prepared with attention to transparency, can be a vital asset in moving a P&T committee towards evidence-based decision making. In our experience, training sessions for P&T committee members that provide the members with an understanding of evidence-based medicine and the important elements of critical appraisal considerations provide tremendous payoffs in terms of the efficiency of committee meetings and the quality of the formulary decisions that are made. Such training also helps to instill trust in the work of the committee staff members who prepare the monographs and class reviews.

The implementation of decisions can be eased if committee members can be engaged as informed opinion leaders to help educate colleagues in their provider communities.

This evidence-based approach to informing formulary decisions is powerful because it provides a solid, scientific basis for making judgments about the validity and clinical usefulness of agents. An evidence-based approach builds on appropriate study design, methodology, and execution and considers the weight of the resulting scientific evidence to inform decisions. This evidence-based approach figures importantly into considerations of overall benefits, risks, therapeutic alternatives, uncertainties, patient and provider satisfaction, costs, and other considerations so that P&T

committee members can make appropriate choices about drugs, including efficacy as related to other agents. Making these choices is a critical step for providing quality and value-based patient care.

**Table 6**
**Key characteristics of a concluding statement in a drug review or monograph**

| Statement component | Data to include |
|---|---|
| Category/purpose of study | Efficacy, safety or other |
| Intervention | Dosing, means of administration, formulation, etc |
| Was demonstrated to be | Superior, equivalent, non-inferior, other [specify] |
| When compared with | Comparator |
| In the following clinically significant area(s) | Indication and end points |
| As measured by | Measurement instruments used |
| Within the following time period | Study duration (intervention to final outcomes measurement) |
| Study population | Describe patient population (inclusions, exclusions, and key baseline characteristics, including demographic details such as ethnicity, gender and age, and other meaningful prognostic characteristics such as relevant medical histories) |
| Results: Absolute | [ARR%], (95% CI [CI, CI%]) |
| Results: Number-Needed-to-Treat | Complete only for statistically significant results |
| **Additional considerations for risk assessment[a]** | |
| Study type | Experimental, observational [specify exact type, eg, RCT, cohort, case report] |
| Risks were | Prespecified, not prespecified, other [specify] |
| Results of important risks reported as statistically significant, plus important risks that are reported as nonsignificant, but are actually "inconclusive" because of a potentially clinically relevant difference within the CI | Risks and study results, including confidence interval |
| Confirmation in additional studies | Yes, no [include references] |

a Important harms may be found only through longer follow-up. There may also be additional risks found through well-done studies of long duration. Newer medications are sometimes found after a year or more to have unsuspected side effects or health risks. Most long-term risks of newly approved medications are not known until physicians discover unsuspected side effects in their patients over time. Clinicians are urged to follow FDA recommendations regarding therapy.

Adapted from the Delfini Evidence Grading Tool.


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