Delfini Evidence Tool Kit
Evidence Synthesis & Clinical Recommendations Tool

Project:
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Contents

Goal

Present your best attempt to summarize the weight of the evidence into a conclusion about usability of the study information you have reviewed and how you recommend that information be applied. You wish to combine scientific strength AND usefulness of the information in order to make decisions about health care. You will need to apply your own judgment.

It may be useful, before you begin your synthesis work, to consider ideal study parameters for the best available evidence so that you have an effective means of comparison between optimal and the research you find. This information can be found in the **Delfini Evidence Grading Tool**.

Introduction to Evidence Synthesis Steps

Systematic Review Attempt	1. We **strongly** recommend that you first acquaint yourself with characteristics of quality systematic reviews using the **Delfini Systematic Review Tool** or another similar guide. Do as many of these steps in the best possible way that you can.
Goals & Ideals	2. Decide upon the goal of your intended clinical recommendation and anticipate parameters of the ideal research methods to answer this question for comparison purposes. (For ideas, see **Ideal Research Study Parameters** in the **Delfini Evidence Grading Tool**.)
Ask & Acquire	3. Frame your clinical question and conduct a systematic search of the medical literature to identify the best possible studies. ▪ Document your searching and your filtering strategy.
Selection Criteria	4. Determine inclusion/exclusion criteria for studies you plan to use in your synthesis.
Appraise for Validity & Results	5. Critically appraise selected studies for both validity and usefulness of results. The goal is to include only those studies that represent the best available valid, usable scientific

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	evidence. There are likely to be few. ▪ We strongly recommend the use of tools. The **Delfini Study Validity & Usability Tool** addresses both validity and results assessment in one tool. ▪ Grade each study. See the **Delfini Evidence Grading Tool.**
Study Selection for Best Available Valid and useful Evidence	6. For studies passing **both** validity and results assessment, rank studies by grade of study, and select those you wish to include. ▪ The **Delfini Validity and Usability Grading Scale** in the **Delfini Evidence Grading Tool** is our suggested means for ranking studies and provides criteria for selecting studies for inclusion in an evidence synthesis, along with providing suggestions for grading the strength of your synthesis.
Harms	7. Because harms may not have been sufficiently addressed in your studies of choice, determine if you need to do a new search specific to learning about any harms of what you wish to recommend. Modify your statement as needed if you have new information.
Synthesize & Summarize	8. Summarize the best available valid and useful evidence. This may be a text statement or a table documenting characteristics of the evidence you have identified as being the best. (A table is included in this tool.) Again, you will have to apply judgment.
Strength & Limitations of Synthesis (Grading & Documentation)	9. Grade the quality of the collective evidence. 10. Document limitations of your assessment or why it differs from other syntheses using criteria for systematic reviews.
Clinical Recommendation	11. Write a clinical recommendation based on your findings. Quantitate where possible. See the **Delfini Evidence Grading Tool** for wording suggestions.
Recommendation Grading & Documentation	12. Label the strength of your recommendation to make as transparent as possible and document the limitations of your assessment using criteria for systematic reviews. See the **Delfini Evidence Grading Tool** for help with grading and judgments.
Analysis	13. Prepare a brief analysis of other considerations such as – ▪ Efficacy versus effectiveness projection ▪ Applicability to which patient population and under which circumstances ▪ Patient perspective (benefits, harms, risks, costs, uncertainties, alternatives) ▪ Physician perspective (e.g., likelihood of acceptance and appropriate application) ▪ Patient acceptance (e.g., likelihood of patient acceptance and adherence) ▪ Actionability (e.g., FDA approved, affordable, do-able, implementable, fits circumstances of care, etc.)

Executive Summary & Format Suggestions

We recommend that a brief executive summary precede the details of your synthesis work (detailed instructions for which follow this table). Suggested contents are as follows:

Categories	**Summary from Cochrane or Clinical Evidence**

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Categories	Summary from Cochrane or Clinical Evidence
Clinical Question	
Background Information	
General Information	
Number of Included Studies	
Number of Subjects	
Population Characteristics	
Homogeneity Information	
Efficacy Summary	
Overall Grade of your summary's usefulness	
Concluding Statement	
"Insufficient Evidence" Summary	
Notes/Other	
Judgments	
Safety Summary	
Overall Grade of your summary's usefulness	
Concluding Statement	
"Insufficient Evidence" Summary	
Notes/Other	
Judgments	
Summary Detail of Findings from Valid Studies	
List out a summary for each study included… ▪ Author ▪ Grade ▪ Brief critique ▪ Quantified results ▪ P-value	
Other	

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Categories	Summary from Cochrane or Clinical Evidence
Limitations of Your Work	
Notes/Other	

Follow the Executive Summary with…

Supporting Documentation

- FDA information
- Evidence synthesis tables
- Search & filtering strategy (efficacy, harms, other)
- Selection criteria for studies
- Methods used to determine validity and usability
- Grading scheme
- Table of included studies
- Critical appraisals of included studies
- Table of excluded studies
- References
- Glossary
- Conflicts of interest
- Reviewers
- Preparers
- Date

Examples for Suggestions for How to Do an Evidence Synthesis

1. Imagine that you have conducted a literature search for a therapy question using Drug X for Condition Y. Your group is interested in adding another agent for women failing Drug Z. You have filtered your search to find the best available valid and useable evidence. You have selected three RCTs to review. They have some variations in their population.
2. You have done a validity review and you have evaluated the results of those studies you have found to be valid. Your assessment of the outcomes and results for Drug X looks like this:

> Study 1. There is Grade A Evidence: Strong evidence of efficacy. It can be concluded that there is a reduction in mortality for non-pregnant women 45 to 60 years of age with condition Y, taking Drug X as compared to placebo within 5 years. The ARR for 5 years is 1.8%, 95% CI (1.25 to 2.5%). NNT for mortality reduction is estimated at NNT of 55, 95% CI (40 to 80)(5 years).
>
> Study 2. There is Grade A Evidence: Strong evidence of efficacy. It can be concluded that there is a reduction in mortality for non-pregnant women 50 to 65 years of age with condition Y taking Drug X as compared to

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placebo within 5 years. The ARR for 5 years is 2%, 95% CI (1 to 3%). NNT for mortality reduction is estimated at NNT of 50, 95% CI (33 to 100) (5 years).

Study 3. Grade UVU Evidence: Uncertain Evidence (Uncertain Validity and Uncertain Usefulness [See Appendix for explanation] .There is uncertain evidence of efficacy (reduction in mortality) and uncertain validity and usefulness due to small sample size, several weaknesses in methodology which indicates that Drug X might be of benefit in non-pregnant women 30 to 44 years of age. The ARR for 5 years is 5%, 95% CI (3 to 7). NNT for mortality reduction is estimated at 20, 95% CI (14 to 33) (5yrs).

3. You decide that you are going to summarize all three of the studies – you will use the "uncertain study" because it is an RCT, there are few threats to validity and the results are going in a consistent direction with the other two good studies.

4. Applying your own judgment, you rate the level of usability of combination of these three studies that you have elected to summarize. You rate the combination of the studies as Grade A, USEFUL, i.e., the weight of the evidence receives an A grade even though study 3 receives an individual grade of UVU. You make this determination because the UVU study is going in the same direction as the Grade A studies, so overall you deem the weight of the information useful.

Grade of Usability	Strength of Evidence
• **Grade A: Useful**	The weight of the evidence appears sufficient to use in making health care decisions. • Several well-designed and conducted studies that consistently show similar results

Note: Because of the Grade UVU study, some groups might elect to give this a Grade B, which is a reasonable choice as well. Evidence grading involves a great deal of judgment.

5. While assessing this information as useful, you realize that you need to apply your own judgment in determining how the information is to be used. Some groups might decide on a conservative approach due to the uncertainty of Study 1 and the likelihood of realizing results smaller than efficacy in the other studies. Such a group might decide to –

   Recommend an interpretation of NNT=50 to 55 (5yrs) for ages 45 to 65, with a statement that there is uncertain evidence of benefit for women 30 to 44 and no evidence for women at other ages.

   Another group might decide to "keep it simple" and recommend an interpretation of NNT=50 (5yrs) for ages 30 to 65. Judgment will vary between evaluators.

6. You would then prepare your text summary or your evidence synthesis table (see below) and quantitative statements.

7. From that you will write a clinical recommendation and document its limitations.

Example of an Evidence Synthesis Table

You may choose to use the following table instead of, or in addition to, an **Evidence Synthesis Text Summary Statement** – see below for the text example.

Item	Example Entry
1. Intervention or Exposure (include	Drug X 4 mg tid

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Item	Example Entry
characteristics and parameters such as dosing)	
2. Grade of Evidence Synthesis	Grade A: Useful
3. Clinical significance: Is there direct evidence of benefit in the following areas? Morbidity, mortality, symptom relief, functioning, health related quality of life	Mortality
4. Population (including disease spectrum, risk groups, etc. and documentation of exclusions)	Women ages 30 to 65 (excluding pregnant women)
5. Indication	With Condition Y
6. Line of therapy	Second line—you have approved Drug Z
7. Comparator	Placebo
8. Head-to-head or equivalence trials (include grade and information about study quality)	None
9. Based on study types	RCTs
10. Quality of studies: ▪ Grade ▪ Number of studies ▪ N ▪ Summary of validity and usefulness ▪ Other key details as applicable	Grade A: Well-done, valid and useful RCTs for women, ages 45 to 65 ▪ Two studies ▪ Total n = 15,432 Grade UVU: Uncertain validity and usability of RCT for women, ages 30 to 44 ▪ 1 study ▪ Total n = 241 ▪ Uncertainty due to small sample size, 2% loss to follow-up and one patient crossed over to therapy
11. Grade and Results (include NNT [CI] and study time period)	▪ Grade A: Women 45 to 65: NNT 50 to 55, 95% CI (33 to 100)(5 yrs) drug X vs placebo ▪ Grade UVU: Women 30 to 44: NNT 20, 95% CI (14 to 33) (5 yrs) drug X vs placebo
12. Uncertainties	▪ Pregnant women since excluded from all studies. ▪ Women of childbearing age due to uncertainty re: fetal effects.
13. Alternatives	None for those failing Drug Z
14. Cost	Equivalent to Drug Z
15. Review Limitations	▪ Unable to do a systematic review, but attempted as many steps as possible. ▪ Did not test for heterogeneity, but did qualitative analysis of homogeneity and did review CI's, RRR and point estimates. ▪ Inclusion of Grade U evidence because of need for help for this population and no better evidence – however, study is going in same direction as Grade A studies
16. Harms	Harms or potential harms may include skin rash. Harms data is not

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Item	Example Entry
	from RCTs. Harms data is from post-marketing surveillance studies (case reports). All studies excluded pregnant women and there are no reports of use specific to pregnant subpopulations.
17. Usability statement (e.g., "There is strong, moderate or uncertain evidence to conclude efficacy.") Considering addressing any exclusions, limiting circumstances, results for the comparator and statements about risks or harms.	There is strong evidence of efficacy. It can be concluded that Drug X in comparison to placebo reduces mortality by approximately 1.8% to 2% 95% CI (1.25 to 2.5%) in women, aged 45 to 65, with Condition Y and who are not pregnant. NNT for prevention of overall mortality is estimated to be 50 to 55, 95% CI (33 to 100) (5 yrs). There is uncertain evidence of efficacy in women, aged 30 to 44 and who are not pregnant, as compared to placebo.
Clinical Recommendation & Other Considerations Based on Evidence Synthesis	
18. Grade for Clinical Recommendation & Reason	Grade B: Possibly Useful We feel the weight of the evidence is Grade A; however, our clinical recommendation includes advice for a younger population which is not strongly supported by this evidence. We apply a conservative approach for this reason.
19. Recommendation for population	Women with Condition Y failing Drug Z and who are not pregnant
20. Under what circumstances	See above
21. Intervention (include characteristics and parameters such as dosing)	Drug X 4 mg tid
22. Projection of efficacy or effectiveness (consider recommendation for downward adjustment of efficacy to effectiveness)	NNT effectiveness for reduction of overall mortality is estimated to be approximately 50 to 55 (5 yrs)
23. Caution on Harms	Patients should be advised of the possibility of rash. Drug should be used conservatively in pregnant women who should be advised of uncertain effects on fetuses due to lack of information.
24. Actionability	Yes
25. Considerations from physician perspective	Should be well-received since there are no reasonable alternatives and good safety profile.
26. Considerations from patient perspective	Should be well-received since there are no reasonable alternatives for patients failing Drug Z and good safety profile.
27. Limitations of Clinical Recommendation	Uncertainty re: population 30 to 44. Chose conservative NNT for effectiveness estimate. Results may be better in practice.
28. Text Statement for Your Clinical Recommendation	For women with condition Y, ages 30 to 65—and who are not pregnant—failing therapy on Drug Z, consider use of Drug X as a second line therapy to reduce mortality—NNT estimate =50 to 55 (5 yrs). This clinical recommendation is rated Grade B: Possibly Useful

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Example of Evidence Synthesis Text Summary Statement

You may choose to use this method instead of, or in addition to, an **Evidence Synthesis Table** – see above for the table example and below for the actual format that you can fill in.

Evidence Synthesis Text Summary Statement: Interpretation of the Weight of the Evidence
This evidence synthesis for Drug X is based on three studies and overall, this evidence is rated as grade A (valid and useful). For women of 45 to 65 years of age, who are not pregnant, with Condition Y evidence is Grade A: Strong Evidence of efficacy. It can be concluded that there is benefit in mortality reduction for women, 45 to 65 years of age with Condition Y taking Drug X when compared to placebo within a 5 year time period as measured by death certificate. The ARR for 5 years is 1.8%, 95% CI (1.25% to 2.5%). NNT for overall mortality reduction is estimated at 50 to 55, 95% CI (40 to 80). Harms or potential harms may include skin rash. There is no statistically significant harms data from RCTs. For women of 30 to 44 years of age, who are not pregnant, with Condition Y evidence is Grade UVU: Uncertain Evidence of efficacy. There is evidence of uncertain validity and usefulness due to small sample size and a few minor threats to validity i.e., 2% loss to follow-up, one patient assigned to placebo but treated with agent, which indicates Drug X might benefit this population, as compared to placebo but this is uncertain. There is one study with reported benefit in mortality reduction for women, 30 to 44 years of age with Condition Y taking Drug X compared to placebo within a 5 year time period as measured by death certificate. The ARR for 5 years is 5%, 95% CI (3% to 7%). NNT for overall mortality reduction is estimated at 20, 95% CI (14 to 33). Harms or potential harms may include skin rash. There is no statistically significant harms data from RCTs. No studies have been done on women younger than 30 or older than 65. **Harms/Risks** Cause and effect can only be concluded from randomized controlled trials (RCTs). Harms data is not from RCTs. Harms data is from post-marketing surveillance studies (case reports). Harms or potential harms may include skin rash. All studies excluded pregnant women and there are no reports of use specific to pregnant subpopulations. Conservative estimates should be applied to adjust for efficacy versus effectiveness.

Example of a Resulting Clinical Recommendation

For women with condition Y, ages 30 to 65 – and who are not pregnant – failing therapy on Drug Z, consider use of Drug X as a second line therapy to reduce mortality – NNT estimate =50 to 55 (5 yrs).

This clinical recommendation is rated Grade B: Possibly Useful

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Note that in this example, the weight of the evidence is given a Grade A, but the resulting clinical recommendation is given a Grade B because of the way in which the UVU study was used to include treatment advice for patients in the younger age category based on more uncertain evidence.

Evidence Synthesis Table

You may choose to use instead of, or in addition to, an **Evidence Synthesis Text Summary Statement**—see above for the text example.

Evidence Synthesis Table	
1. Intervention or Exposure (include characteristics and parameters such as dosing)	
2. Grade of Evidence Synthesis	
3. Clinical significance: Is there direct evidence of benefit in the following areas? Morbidity, mortality, symptom relief, functioning, health related quality of life	
4. Population (including disease spectrum, risk groups, etc. and documentation of exclusions)	
5. Indication	
6. Line of therapy	
7. Comparator	
8. Head-to-head or equivalence trials (include grade and information about study quality)	
9. Based on study types	
10. Quality of studies: ▪ Grade ▪ Number of studies ▪ N ▪ Summary of validity and usefulness ▪ Other key details as applicable	

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11. Grade and Results (include NNT [CI] and study time period)	
12. Uncertainties	
13. Alternatives	
14. Cost	
15. Review Limitations	
16. Harms	
17. Usability statement (e.g., "There is strong, moderate or uncertain evidence to conclude efficacy.") Considering addressing any exclusions, limiting circumstances, results for the comparator and statements about risks or harms.	
Clinical Recommendation & Other Considerations Based on Evidence Synthesis	
18. Grade for Clinical Recommendation & Reason	
19. Recommendation for population	
20. Under what circumstances	
21. Intervention (include characteristics and parameters such as dosing)	
22. Projection of efficacy or effectiveness (consider recommendation for downward adjustment of efficacy to effectiveness)	
23. Caution on Harms	
24. Actionability	
25. Considerations from physician perspective	
26. Considerations from patient perspective	
27. Limitations of Clinical Recommendation	
28. Text Statement for Your Clinical Recommendation	