

Module 17: Applying the results – trade-offs, adverse effects and outcomes

CAUTION!! This module is not up to date.

Authors **MUST** refer to ‘Chapter 11: Presenting results and ‘Summary of findings’ tables’ in the *Cochrane Handbook for Systematic Reviews of Interventions* for current information.

This module will discuss the stage in a review when, having analysed and presented the results, we are trying to interpret their application to clinical practice and policy.

Learning objectives

- Understand the necessary (but 'insufficient') role of systematic reviews in making decisions about health care
- Appreciate that the balance between benefit and risk may be different for different groups and different individuals
- Understand the limitations of systematic reviews in identifying all adverse effects and be aware of other sources of information which are more likely to be able to identify possible adverse effects
- Be aware of the problems in interpreting subjective outcomes
- Appreciate the need for caution in interpreting and applying results from surrogate outcomes

Relevant sections of the *Cochrane Handbook for Systematic Reviews of Interventions*

- Section 12.3: Issues in applicability
- Chapter 11: Presenting results and ‘Summary of findings’ tables

Where does this go in a Cochrane review?

- The Inclusion Criteria section of the review should describe all the outcomes (both benefits and harms) that you will consider in the review
- The Discussion section of the review should describe how you have interpreted the results, in particular the strength of evidence about all the outcomes, clarification of any important trade-offs between the expected benefits, harms and costs of the intervention, as well as any other considerations that might be relevant to someone making a decision

Evidence of effectiveness alone is not enough for making decisions



Activity: Write a list of all the factors that need to be taken into account when making a health care decision

Think about the decision of whether or not to use beta-interferon for people with multiple sclerosis. This is a relatively new drug for a condition which can progress, and for which few other treatments are available. Try to write down a list of all the factors that come into your mind when you are trying to make a health care decision like this.

Your list probably has many factors, among which will (hopefully) be evidence about whether the treatment improves the outcome for people with multiple sclerosis. But I imagine your list would probably include things like any special needs of the user, their priorities and values, as well as the available resources. You may have many other things on your list as well.

The key point is that research evidence is only one factor, albeit an important one, that needs to be taken into account during the decision-making process. Other types of evidence, such as the needs of the user, their priorities and values, as well as the available resources also need to be considered in the decision-making process.

It is not the job of the reviewer to try to weigh up all those factors, because a reviewer can never take account of all the variation in all the factors in the list in all the places that the review will be used. It is, however, possible to assist the user of your review in how to interpret and apply the evidence.

In the previous module we began the task of interpreting the results by considering the strength and relevance of the evidence. Even with this information the ultimate decision as to how to apply the evidence will be up to the users of the review. We need to remember that users of reviews will often come from very different settings around the world with very different circumstances and backgrounds. In this module we explore some of the other things that we can do to help users decide how to apply the evidence.

Identifying all the possible outcomes

A useful starting point is to identify all the outcomes that were considered in the review. These should have been listed with the inclusion criteria for studies in the review. It is often a good idea to have a further check that you haven't missed any important outcomes. For example, reviewers often unintentionally focus on the positive effects of treatment and forget the possible adverse effects.

In many reviews it may be important to consider the cost of treatment as one of the outcomes. Undertaking formal economic evaluations of the costs and benefits of an intervention are beyond the scope of the standard review. However, increasingly systematic reviews are being used as part of economic analyses.

Drawing up a balance sheet



Activity: Draw up a balance sheet listing all the outcomes that might need to be considered

A useful tip is to draw up a balance sheet where you list all the “beneficial” (or positive) effects associated with the intervention on one side, and all the potential “harms” (or negative) outcomes on the other side.

Take the example of whether or not to treat a sore throat with antibiotics (when we don’t know for sure what is causing it). The potential positive effects of treatment include:

- Reduction in severity of illness
- Reduction in pain
- Reduction in the duration of illness
- Reduction in infections following on (such as sinusitis, and acute otitis media)
- Reduction in subsequent noninfective complications (such as rheumatic fever and acute glomerulonephritis (an acute inflammation of the kidney)).

The potential negative effects of treatment include:

- Adverse effects of antibiotics (such as diarrhoea, thrush etc).
- The cost to society in terms of antibiotic prescription and overuse

Sometimes the labeling of outcomes can be subjective, depending on the perspective you are coming from. Take the example of an intervention for Alzheimer’s disease. If the intervention improves mobility, this might be seen as a positive effect from a patient’s perspective, but a negative effect from a carer’s perspective.

What if there are no data available on some outcomes?

It may be that there are no data available on some of the outcomes. For example, some of the slow onset or more rare beneficial or adverse effects associated with treatments are unlikely to be seen in trials with relatively short-term follow-up or with small numbers of participants. It is often necessary to consider other types of data (such as from long term cohort studies or post marketing surveillance studies) in order to obtain reliable data on potential harms. To do this thoroughly, however, adds a whole new dimension to a systematic review, as we would have to search for these studies and then appraise and combine them. At the moment few Cochrane reviews do this.

Remember to list all possible outcomes even if there are no data available

If you have insufficient information about particular outcomes, this should be clearly stated in your review. If you feel these outcomes are important you may suggest that they are included in future trials by discussing them in the “Implications for Research” section of your review.

What do users of reviews need to know about these outcomes?

Absolute risk reduction is often more meaningful to users than relative risk reduction

The natural history of a disease may be important

We have seen, in Module 11, the importance of knowing the absolute change (not just the relative change) in the probability of each outcome as a result of the intervention. However, in order for users in different settings to decide how to apply this information, they also need to know how common the outcome is in their particular setting. To come back to the example we used for the balance sheet, in most developed countries the risk of rheumatic fever or acute glomerulonephritis as a complication of sore throat is extremely low, however, in many developing countries the risk is much greater to begin with, and even a small reduction in the absolute probability of this outcome may be very important.

In other instances, it may be important for the user to know the natural history of the condition. For example, with many self-limiting illnesses, a one day reduction in symptom duration, while it may be statistically significant, needs to be set against an illness which may only last for four or five days at most.

Try to avoid value judgments

Value judgments are any statements where you make assumptions about the value placed on particular outcomes. An easy way to spot them is to ask yourself “Would everyone agree with this statement?” If the answer is probably not, then it may be best to not make that judgment in your review. It’s better to present the data in a way that will allow the user to make a balanced objective ‘trade-off’ given their own personal circumstances. A one day reduction in the duration of an illness may mean a lot to a particular user, where others will be willing to accept that extra day’s illness in return for reducing their chance of some other outcome (for example, the side effects of the intervention).

Ask the question: Can the results apply in my situation?

People in many different situations will use your review. It is important that you write the review in a way which will allow individuals to decide whether your review applies to them.

First, a user has to decide whether the review provides valid information about the potential benefits and harms that may be important to them. Then they need to decide whether the participants and settings in the included studies are reasonably similar to their own situation. It is often helpful for users to consider asking themselves whether there are any good reasons why the evidence should not be applied in their situation. Some of these reasons might be related to:

- Biological and cultural variation
- Variation in compliance
- Variation in the baseline risk



Reading: section [12.3](#) of the *Cochrane Handbook for Systematic Reviews of Interventions* explains how to decide whether results apply in different situations

These are explained further in section 12.3 of the *Cochrane Handbook for Systematic Reviews of Interventions*, which you should read now.



Activity: List specific factors relevant to your review which might influence whether the results can be applied in a different setting

Now try to think of some examples where these factors might influence the applicability of the findings from your own review and write these down. An example would be that if the trials in your review are done in a developed country with good access to diagnostic equipment, and the reader of your review is a doctor trying to decide to whether to implement the treatment in a resource poor country where the equipment available to determine diagnosis is not available, and there are no trials in your review performed in participants similar to the people she treats, the results of your review may not help her make this decision.

If you have come up with any factors that might limit the applicability of your own review these might be worth highlighting in the Discussion.



Activity: Make a list of reasons why the results of different studies within a review might vary

How consistent are the results?

There are many reasons why the results of studies included within a review may vary (even if there is no heterogeneity detected with statistical testing). For example, in a review of giving smoking cessation advice, we found a considerable variation in the results depending on the intensity of the advice and follow-up provided. Other reasons why results may vary include differences in the participants (for example, their age, gender, or presence of some biochemical marker) or differences in their underlying disease status. You should have an idea of the possible reasons why the results of the trials in your review might vary from thinking about it in the module on heterogeneity. If these differences might be clinically relevant they would be worth highlighting when discussing the evidence in your review.

A word of caution

Some chance variation between different subgroups is inevitable. It is often a trap to try to explore variation in results by undertaking separate analyses of different sub-groups. You should avoid doing this unless there was a good prior reason to believe that a particular sub-group might respond differently to the intervention.

Other useful information

Is there other information which may be helpful for a user to have

Often there may be some other information that might be useful to consider when discussing the results of a review. For example, it might help to include some information about the size or frequency of a particular health care problem that the review is addressing. However, you need to be quite careful because this information may be very context specific and might be better addressed at a more local level. Much as it would be good if we could provide users of a review with all the information they require to make a decision, this is rarely (if ever) possible.

There are more formal ways of using the evidence and considering benefits, harms, patient preferences and other factors specific to your particular setting. These tools, often termed decision analyses or decision trees, are outside the scope of this material, but often draw on evidence provided by Cochrane Reviews.

Checklist for your Discussion

A final check

At the end of the discussion section it is worth re-reading and asking yourself:

- Have all the main outcomes been considered?
- Have data been presented about the absolute change as a result of the intervention for all possible outcomes?
- Have I considered any factors that might limit the application of these results in different situations?
- Are these results consistent across the included studies or do they vary for some reason?
- Have I avoided making value judgments about how to interpret my findings?

TO BE REVISED