**13.1.2  Why consider non-randomized studies?**

The Cochrane Collaboration focuses particularly on systematic reviews of randomized trials because they are more likely to provide unbiased information than other study designs about the differential effects of alternative forms of health care. Reviews of NRS are only likely to be undertaken when the question of interest cannot be answered by a review of randomized trials. The NRSMG believes that review authors may be justified in including NRS which are moderately susceptible to bias. Broadly, the NRSMG considers that there are three main reasons for including NRS in a Cochrane review:

a)      To examine the case for undertaking a randomized trial by providing an explicit evaluation of the weaknesses of available NRS. The findings of a review of NRS may also be useful to inform the design of a subsequent randomized trial, e.g. through the identification of relevant subgroups.

b)      To provide evidence of the effects (benefit or harm) of interventions that cannot be randomized, or which are extremely unlikely to be studied in randomized trials. In these contexts, a disinterested (free from bias and partiality) review that systematically reports the findings and limitations of available NRS can be useful.

c)      To provide evidence of effects (benefit or harm) that cannot be adequately studied in randomized trials, such as long-term and rare outcomes, or outcomes that were not known to be important when existing, major randomized trials were conducted.

Three other reasons are often cited in support of systematic reviews of NRS but are poor justifications:

d)      Studying effects in patient groups not recruited to randomized trials (such as children, pregnant women, the elderly). Although it is important to consider whether the results of trials can be generalized to people who are excluded from them, it is not clear that this can be achieved by consideration of non-randomized studies. Regardless of whether estimates from NRS agree or disagree with those of randomized trials, there is always potential for bias in the results of the NRS, such that misleading conclusions are drawn.

e)   To supplement existing randomized trial evidence. Adding non-randomized to randomized evidence may change an imprecise but unbiased estimate into a precise but biased estimate, i.e. an exchange of undesirable uncertainty for unacceptable error.

f)    When an intervention effect is really large. Implicitly, this is a result-driven or *post hoc* justification, since the review (or some other synthesis of the evidence) needs to be undertaken to observe the likely size of the effects. Whilst it is easier to argue that large effects are less likely to be completely explained by bias than small effects (Glasziou 2007), for the practice of health care it is still important to obtain unbiased estimates of the magnitude of large effects to make clinical and economic decisions (Reeves 2006). Thus randomized trials are still needed for large effects (and they need not be large if the effects are truly large). There may be ethical opposition to randomized trials of interventions already suspected to be associated with a large benefit as a result of a  systematic review of NRS, making it difficult to randomize participants, and interventions postulated to have large effects may also be difficult to randomize for other reasons (e.g. surgery vs. no surgery). However, the justification for a  systematic review of NRS in these circumstances should be classified as (b), i.e. interventions that are unlikely to be randomized, rather than as (f).

### 13.1.3  Key issues about the inclusion of non-randomized studies in a Cochrane review

Randomized trials are the preferred design for studying the effects of healthcare interventions because, in most circumstances, the randomized trial is the study design that is least likely to be biased. Any Cochrane review must consider the risk of bias in individual primary studies, including both the likely direction and magnitude of bias (see Chapter [8](https://handbook-5-1.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm)). A review that includes NRS also requires review authors to do this. The principle of considering risk of bias is exactly the same. However, potential biases are likely to be greater for NRS compared with randomized trials. Review authors need to consider (a) the weaknesses of the designs that have been used (such as noting their potential to ascertain causality), (b) the execution of the studies through a careful assessment of their risk of bias, especially (c) the potential for selection bias and confounding to which all NRS are suspect and (d) the potential for reporting biases, including selective reporting of outcomes.

Susceptibility to selection bias (understood in this *Handbook* to mean differences in the baseline characteristics of individuals in different intervention groups, rather than whether the selected sample is representative of the population) is widely regarded as the principal difference between randomized trials and NRS. Randomization with adequate allocation sequence concealment reduces the possibility of systematic selection bias in randomized trials so that differences in characteristics between groups can be attributed to chance. In NRS, allocation to groups depends on other factors, often unknown. Confounding occurs when selection bias gives rise to imbalances between intervention and control groups (or case and control groups in case-control studies) on prognostic factors, i.e. the distributions of the factors differ between groups *and* the factors are associated with outcome. Confounding can have two effects in a meta-analysis: (a) shifting the estimate of the intervention effect (systematic bias) and (b) increasing the variability of the observed effects, introducing excessive heterogeneity among studies (Deeks 2003). It is important to consider both of these possible effects (see Section [13.6.1](https://handbook-5-1.cochrane.org/chapter_13/13_6_1_whats_different_when_including_non_randomized_studies.htm)). Section [13.5](https://handbook-5-1.cochrane.org/chapter_13/13_5_assessing_risk_of_bias_in_non_randomized_studies.htm) provides a more detailed discussion of susceptibility to bias in NRS.

### 13.6.1  What is different when including non-randomized studies?

Review authors should expect greater heterogeneity in a systematic review of NRS than a systematic review of randomized trials. This is due to the increased potential for methodological diversity through variation between primary studies in their risk of selection bias, variation in the way in which confounding is considered in the analysis and greater risk of other biases through poor design and execution. There is no way of controlling for these biases in the analysis of primary studies and no established method for assessing how, or the extent to which, these biases affect primary studies (but see Chapter [8](https://handbook-5-1.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm)).

There is a body of opinion that it is appropriate to pool results of non-randomized studies when they have large effects, but the logic of this view can be questioned. NRS with large effects are as likely (perhaps more likely) to be biased and to be heterogeneous as NRS with small effects. Judgements about the risk of bias and heterogeneity should be based on critical appraisal of the characteristics and methods of included studies, not on their results.

When assessing similarity of studies prior to a meta-analysis, review authors should also keep in mind that some features of studies, for example assessment of outcome not masked to intervention allocation, may be relatively homogeneous across NRS but still leave all studies at risk of bias.

If authors judge that included NRS are both reasonably resistant to biases and relatively homogeneous in this respect, they may wish to combine data across studies using meta-analysis (Taggart 2001). Unlike for randomized trials, it will usually be appropriate to analyse adjusted, rather than unadjusted, effect estimates, i.e. analyses that attempt to ‘control for confounding’. This may require authors to choose between alternative adjusted estimates reported for one study. Meta-analysis of adjusted estimates can be performed as an inverse-variance weighted average, for example using the ‘Generic inverse-variance’ outcome type in RevMan (see Chapter 9, Section [9.4.3](https://handbook-5-1.cochrane.org/chapter_9/9_4_3_a_generic_inverse_variance_approach_to_meta_analysis.htm)). In principle, any effect measure used in meta-analysis of randomized trials can also be used in meta-analysis of non-randomized studies (see Chapter 9, Section [9.2](https://handbook-5-1.cochrane.org/chapter_9/9_2_types_of_data_and_effect_measures.htm)), although the odds ratio will commonly be used as it is the only effect measure for dichotomous outcomes that can be estimated from case-control studies, and is estimated when logistic regression is used to adjust for confounders.

One danger is that a very large NRS of poor methodological quality (for example based on routinely collected data) may dominate the findings of other smaller studies at less risk of bias (perhaps carried out using customized data collection). Authors need to remember that the confidence intervals for effect estimates from larger NRS are less likely to represent the true uncertainty of the observed effect than are the confidence intervals for smaller NRS (see Section [13.5.1.2](https://handbook-5-1.cochrane.org/chapter_13/13_5_1_2_evidence_of_risk_of_bias_in_non_randomized_studies.htm)), although there is no way of estimating or correcting for this.

KMC is associated with decreased mortality among

newborns who survive to receive it, particularly among LBW infants.

This study allowed the combination and potential differentiation of gestational age, longer term outcomes and sub group analyses. Raised questions regarding the direction for further studies.

Interestingly, I was surprised of no mention of the impact of high versus low risk of bias studies on findings nor any discussion of impact of including NRS to RS. This would have provided considerable strength to the conclusions.

The findings were in keeping with previous reports of RS only.

No where in the main body of the paper did they differentiate RCTs from observational stuies in contrast to this review examining probiotics

Nor did they provide insight on overall RoB across studies.