Analysis in EPOC reviews

See also Synthesising results when it does not make sense to do a meta-analysis and Interrupted time series (ITS) analyses

Review authors can obtain advice regarding the analysis for their review from their contact editor. Some general suggestions regarding analytic methods used in EPOC reviews are provided below.

Measures of treatment effect

For dichotomous outcomes, if possible, the risk ratio (RR) from statistical analyses adjusting for baseline differences (such as Poisson regressions or logistic regressions) or the ratio of risk ratios (i.e. the risk ratio post intervention / risk ratio pre intervention) should be reported. For continuous variables, if possible, the absolute change from a statistical analysis adjusting for baseline differences (such as regression models, mixed models or hierarchical models) or the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute post-intervention difference between the intervention and control groups - the absolute pre-intervention difference between the intervention and control groups) / the post-intervention level in the control group) should be reported. Review authors considering undertaking a meta-analysis of continuous outcomes that require standardisation across studies (e.g. as standardised mean differences) should have statistical support.

Interrupted time series (ITS) and repeated measure (RM) studies

The preferred analysis method for ITS and RM studies is either a regression analysis with time trends before and after the intervention, which adjusted for autocorrelation and any periodic changes, or ARIMA analysis. The results for the outcomes should be presented as changes along two dimensions: Change in level and change in slope. Change in level is the immediate effect of the intervention and is measured as the difference between the fitted value for the first post intervention data point (one month after the intervention) minus the predicted outcome one month after the intervention based on the pre-intervention slope only.

Change in slope is the change in the trend from pre to post intervention, reflecting the "long" term effect of the intervention. Since the interpretation of change in slope can be difficult, we suggest presenting the long-term effects similar to the way immediate effects are calculated and presented. For example, the effects after half a year (or one year or two years) can be presented as the difference between the fitted value for the sixth month post intervention data point (half a year after the intervention) minus the predicted outcome six months after the intervention based on the pre-intervention slope only. For expenditures it also may be desirable to calculate the costs or

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savings after a half year, one year and two years as the area between the predicted expenditures curves and the actual expenditures.

Review authors should define a transition phase to use for ITS and RM studies that do not define a transition phase, and exclude transition phase data.

If papers with ITS design do not provide an appropriate analysis or reporting of results, but present the data points in a scannable graph or in a table, it is possible to reanalyse the data using methods described in Ramsay 2003.[1] The following segmented time series regression model can be used:

$$Y(t) = B0 + B1*Preslope + B2*Postslope + B3*intervention + e(t)$$

where Y(t) is the outcome in month t. Pre slope is a continuous variable indicating time from the start of the study up to the last point in the pre intervention phase and coded constant thereafter. Post slope is coded 0 up to and including the first point post intervention and coded sequentially from 1 thereafter. Intervention is coded 0 for pre intervention time points and 1 for post intervention time points. In this model, B1 estimates the slope of the pre intervention data, B2 estimates the slope of the post intervention data and B3 estimates the change in level of outcome as the difference between the estimated first point post intervention and the extrapolated first point post intervention if the pre intervention line was continued into the post intervention phase. The difference in slope is calculated by B2-B1. The error term e(t) is assumed to be first order autoregressive. Confidence intervals (95%) can be calculated for all effect measures.

In a repeated measures design, the data are repeated outcome measures from many individuals. If a study does not report appropriate results, we suggest not reanalysing the data from the summary graphs, because no estimate of within patient variability can be obtained from the summary graphs and any reanalysis would underestimate or overestimate the standard error of the effect sizes. Therefore, for RM studies review authors should present the results reported in the original papers only.

Unit of analysis issues

Analyses performed at the same level as the allocation will avoid unit-of-analyses errors.

For clustered designs (such as cluster randomised trials) the reported results in included studies will often be on another level than the level of allocation. If this is the case, an analysis adjusting for clustering should be performed in order to avoid unit-of-analyses errors. When extracted results are not based on analyses adjusted for clustering a reanalysis of the results is required. For further guidance on how to do this, please refer to Section 16.3 of the Cochrane Handbook for Systematic Reviews of Interventions.

If there is a unit of analysis error in the reported analysis for a study and there is insufficient information to reanalyse the results, review authors should contact the authors to obtain necessary

[1] Ramsay CR, Matowe L, Grilli R, Grimshaw JM, Thomas RE. Interrupted time series design in health technology assessment. Int J Technol Assess Health Care 2003;19(4):613-623.

data. If these data are not available, they should not report confidence intervals or p-values for which there is a unit of analysis error.

Dealing with missing data

Review authors should contact authors of included papers if important data are not available. If they are not able to obtain missing data, they should report the results that are available, provided they are not likely to be misleading (e.g. if there is a unit of analysis error).

Assessment of heterogeneity

Review authors should describe how variation in the questions asked by the included studies will be assessed (i.e. what characteristics of the study populations, interventions, outcome measures and settings will be described). Methods for assessing statistical heterogeneity (variation in the results of the studies included in a meta-analysis) should be stated (e.g. visually, using I^2, using a chi-squared test).

Assessment of reporting biases

Consideration should be given to using a funnel plot to assess the risk of publication bias, provided there are a sufficient number of studies.

Data synthesis

If a meta-analysis is planned, the choice between fixed effect and random effects models should be based on the likely extent of variation in the questions asked in different studies (differences in the study populations, interventions, outcome measures or settings) rather than on the observed statistical heterogeneity of results. Review authors should consider whether they expect the true effect to be the same for included studies or they expect the true effects to be related but not the same for included studies. If the true effect is expected to be the same across studies included in a meta-analysis, then a fixed effect model should be used. Otherwise a random effects model should be used or a meta-analysis should not be done (if the populations, interventions, outcome measures or settings differ so much that an average effect across studies would not be helpful).

If a review includes more than one type of interventions, categories of similar interventions should be specified. A table should be prepared for each category of interventions. These tables should include, for example, study identification, the key explanatory factors, and results for one or more outcomes. The primary analyses will often be qualitative analyses based on these tables, including an analysis of the mechanisms through which the interventions were intended to affect the outcome and postulated mechanisms for other affects, both intended and unintended. What is known about the effects of alternative interventions should be summarised within each category, including important interventions for which no evaluations are found. The certainty of the evidence for

estimates of effects should be graded using the approach recommended by the GRADE Working Group (see Worksheets for preparing a summary of findings using GRADE).

In addition, review authors should identify important factors that should be taken into consideration by anyone contemplating implementing an intervention, including: possible trade-offs (of the expected benefits versus harms and costs), the certainty of the available evidence, possible differences in baseline risk and other important factors that might affect the translation of the available evidence into practice in specific settings (see Implications for practice).

Subgroup analysis and investigation of heterogeneity

If there are sufficient numbers of comparisons for similar outcomes across studies, review authors may want to use graphical displays (bubble and whisker plots) to visually explore heterogeneity of the results across studies. They should specify potential explanatory factors that will be considered in the protocol, including explanations about why an interaction is hypothesised and a clear hypothesis about the direction of the interaction (i.e. in which subgroup would the effect be expected to be larger and why?). The visual analyses should be supplemented with multivariate statistical analyses (meta-regression), if appropriate, to examine how the size of observed effects are related to the specified explanatory factors. Several methods for performing meta-regression exist. It is important to specify the method and software that will be used.

Sensitivity analysis

Review authors should consider performing sensitivity analyses for missing data by imputing a plausible range of assumptions. The potential implications of missing information should be discussed. They should also perform sensitivity analyses if there are studies with differing risks of bias that address the same question by excluding studies with a high risk of bias. In addition, any methodological decisions (e.g. choice of intra cluster coefficient (ICC) for reanalysis of cluster randomised trials or inclusion/exclusion of studies from analyses based on pre-specified criteria such dropout rates > 20%) taken in the course of preparing the review should be checked for stability of results in a sensitivity analysis.