



Title **How Important Are Comprehensive Literature Searches and the Assessment of Trial Quality in Systematic Reviews? Empirical Study**

Agency **NCCHTA, National Coordinating Centre for Health Technology Assessment**
Mailpoint 728, Boldrewood, University of Southampton, Southampton SO16 7PX, United Kingdom
tel: +44 2380 595586, fax: +44 2380 595639

Reference Health Technol Assess 2003; 7(1). Jan 2003. www.ncchta.org/execsumm/summ701.htm

Aim

1) To examine the characteristics of difficult-to-locate clinical trials and lower-quality trials. 2) To compare, within meta-analyses, the treatment effects reported in difficult-to-locate trials with those in more accessible trials, and of trials of lower quality with trials of higher quality. 3) To assess the impact of excluding difficult-to-locate trials and lower-quality trials on pooled effect estimates, p-values, and the shape of funnel plots.

Conclusions and results

In total, 159 systematic reviews met the inclusion criteria, but not all included difficult-to-locate trials. Comparisons of treatment effects were based on: unpublished vs published; other languages vs English; non-indexed vs MEDLINE-indexed. Analyses of trial quality were based on: inadequately concealed/unclear vs adequately concealed; not double-blind vs double-blind. The importance of difficult-to-locate trials appears to vary across medical specialties. Unpublished trials show less beneficial effects than published trials whereas non-English language trials and non-indexed trials tend to show larger treatment effects. Trials that are difficult to locate tend to be smaller and of lower methodological quality than trials that are easily accessible and published in English. Trials with inadequate or unclear concealment of allocation show more beneficial effects than adequately concealed trials. Similarly, open trials tend to be more beneficial than double-blind trials. In most meta-analyses, exclusion of trials with inadequate or unclear concealment and trials without double-blinding led to a change (often substantial) toward less beneficial treatment effects. Including unpublished trials reduces funnel plot asymmetry whereas including trials published in languages other than English and non-indexed trials increases the degree of asymmetry in the funnel plot. The impact of trials of lower methodological quality on the funnel plot is substantial for trials with inadequate or unclear concealment of allocation.

Recommendations

Systematic reviews based on searching the English language literature accessible in major bibliographic databases will often produce results close to those obtained from reviews based on more comprehensive searches that are free of language restrictions. The finding that difficult-to-locate trials are often of lower quality raises the worrying possibility that rather than preventing bias through extensive literature searches, bias could be introduced by including trials of low methodological quality. The results confirm that the funnel plot and the regression method to assess funnel plot asymmetry are useful to detect the tendency for smaller studies in a meta-analysis to show larger treatment effects.

Methods

Eight medical journals that regularly publish systematic reviews, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness and the Health Technology Assessment database were searched for relevant articles. Meta-analyses of therapeutic or preventive interventions based on comprehensive literature searches and which combined the binary outcomes of at least 5 controlled clinical trials were included. Language was assessed using the SERLINE journals database, and published trials were classified according to whether or not they had been published in a MEDLINE-indexed journal. Quality assessment was restricted to trials included in Cochrane reviews.

Further research/reviews required

Four main areas are described fully in the report

Written by Professor Matthias Egger, Department of Social Medicine, University of Bristol, UK