

## Systematic review to determine whether participation in a trial influences outcome

Gunn Elisabeth Vist, Kåre Birger Hagen, P J Devereaux, Dianne Bryant, Doris Tove Kristoffersen, Andrew David Oxman

### Abstract

**Objective** To systematically compare the outcomes of participants in randomised controlled trials (RCTs) with those in comparable non-participants who received the same or similar treatment.

**Data sources** Bibliographic databases, reference lists from eligible articles, medical journals, and study authors.

**Review methods** RCTs and cohort studies that evaluated the clinical outcomes of participants and comparable non-participants who received the same or similar treatment.

**Results** Five RCTs (six comparisons) and 50 cohort studies (85 comparisons) provided data on 31 140 patients treated in RCTs and 20 380 comparable patients treated outside RCTs. In the five RCTs, in which patients were given the option of participating or not, the comparisons provided limited information because of small sample sizes (a total of 412 patients) and the nature of the questions considered. 73 dichotomous outcomes were compared, of which 59 reported no statistically significant differences. For patients treated within RCTs, 10 comparisons reported significantly better outcomes and four reported significantly worse outcomes. Significantly heterogeneity was found ( $I^2 = 89\%$ ) among the comparisons of 73 dichotomous outcomes; none of our a priori explanatory factors helped explain this heterogeneity. The 18 comparisons of continuous outcomes showed no significant differences in heterogeneity ( $I^2 = 0\%$ ). The overall pooled estimate for continuous outcomes of the effect of participating in an RCT was not significant (standardised mean difference 0.01, 95% confidence interval -0.10 to 0.12).

**Conclusion** Participating in RCTs neither harms nor benefits participants, compared with receiving the same or similar treatment outside such trials.

### Introduction

Few reviews have considered whether it is beneficial or harmful to participate in randomised controlled trials (RCTs).<sup>1-4</sup> Therefore it remains unclear whether participants in randomised controlled trials benefit directly or whether such studies are solely for the ben-

efit of future patients. Much scepticism also surrounds the applicability of the results to usual practice.<sup>5</sup>

We determined whether the outcomes of participants in RCTs differed from those of comparable non-participants who received the same or similar treatment.

### Methods

We included studies that compared participants in RCTs with comparable non-participants who received the same or similar treatment. Our study included observational studies and RCTs in which participation or the option of participation was randomly allocated.

We searched PubMed, the Cochrane central register of controlled trials, Medline, Embase, the Cochrane methodology register, and PsycINFO; our personal files; and the reference lists of relevant articles, and we hand searched five medical journals. We contacted the studies authors for data on eligible non-participants, and also contacted experts.

Two reviewers independently assessed each article for eligibility and two reviewers independently abstracted data from relevant studies. Studies were assessed for selection bias, detection bias, and exclusion bias. On the basis of the combined risks of the three biases, we grouped each comparison into quality groups for analysis.

We compared the experimental group of the RCT with their respective eligible non-participants who received the treatment and the control group and eligible non-participants who received the control treatment. For each comparison, we analysed the main outcome; when mortality was reported, we analysed it separately. We analysed the dichotomous and continuous results separately. The results are reported as relative risks with 95% confidence intervals, with adjusted estimates when available. Heterogeneity was assessed by  $\chi^2$  test and the  $I^2$  statistic.<sup>6</sup> For the unadjusted relative risk analysis, we used the Mantel-Haenszel test. A fixed effect model was used to calculate summary statistics if

Editorial by Sackett

Norwegian Health Services Research Centre, PO Box 7004, 0130 Oslo, Norway

Gunn Elisabeth Vist  
senior researcher

Doris Tove Kristoffersen  
statistician

Andrew David Oxman  
researcher

National Research Centre for Rehabilitation in Rheumatology, Diakonhjemmet Hospital, Oslo  
Kåre Birger Hagen  
senior researcher

Clinical Epidemiology and Biostatistics, McMaster University Health Sciences Centre, Hamilton, Ontario, Canada

P J Devereaux  
senior researcher  
Dianne Bryant  
senior researcher

Correspondence to: G E Vist  
gev@nhsrc.no

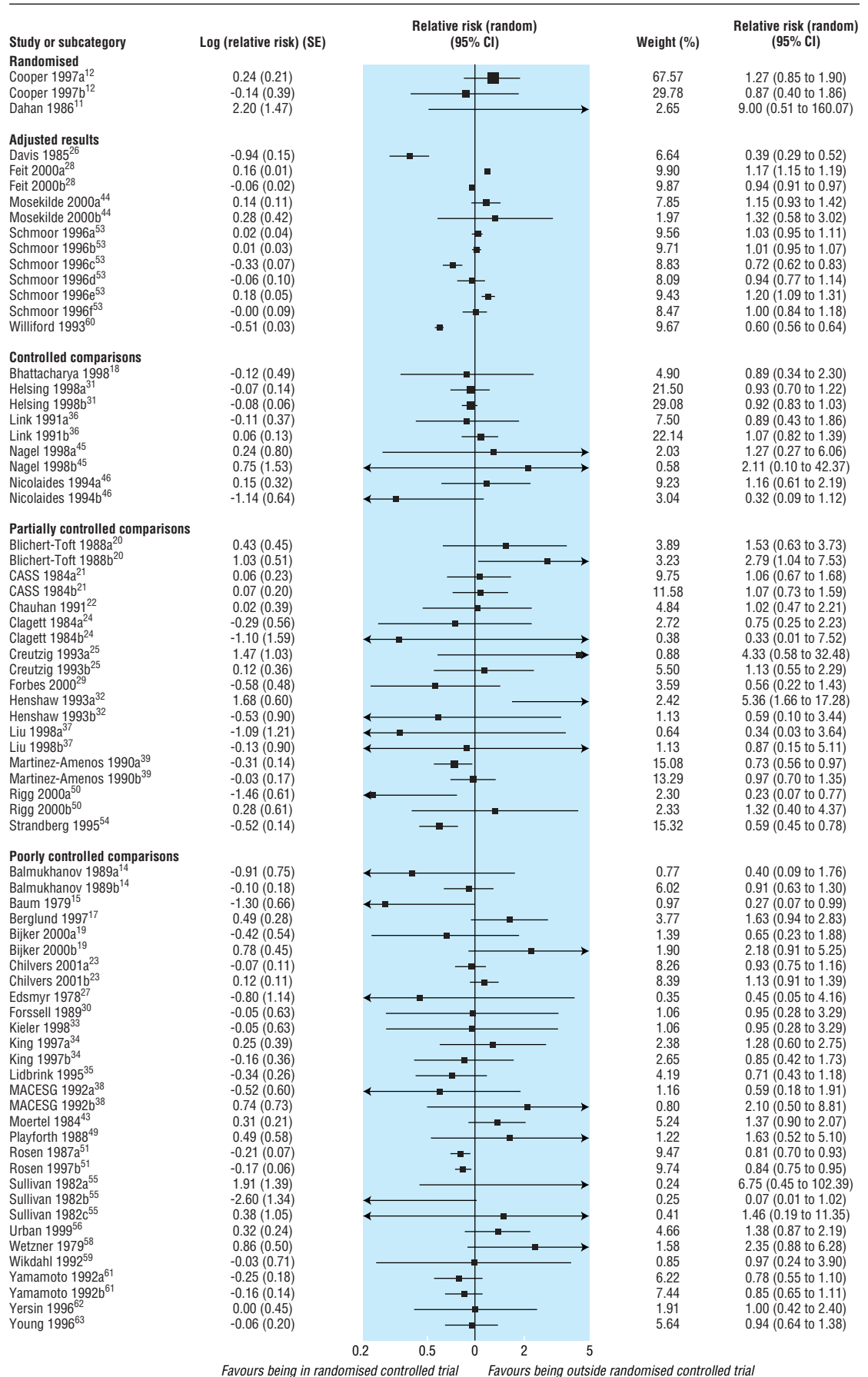
BMJ 2005;330:1175-9



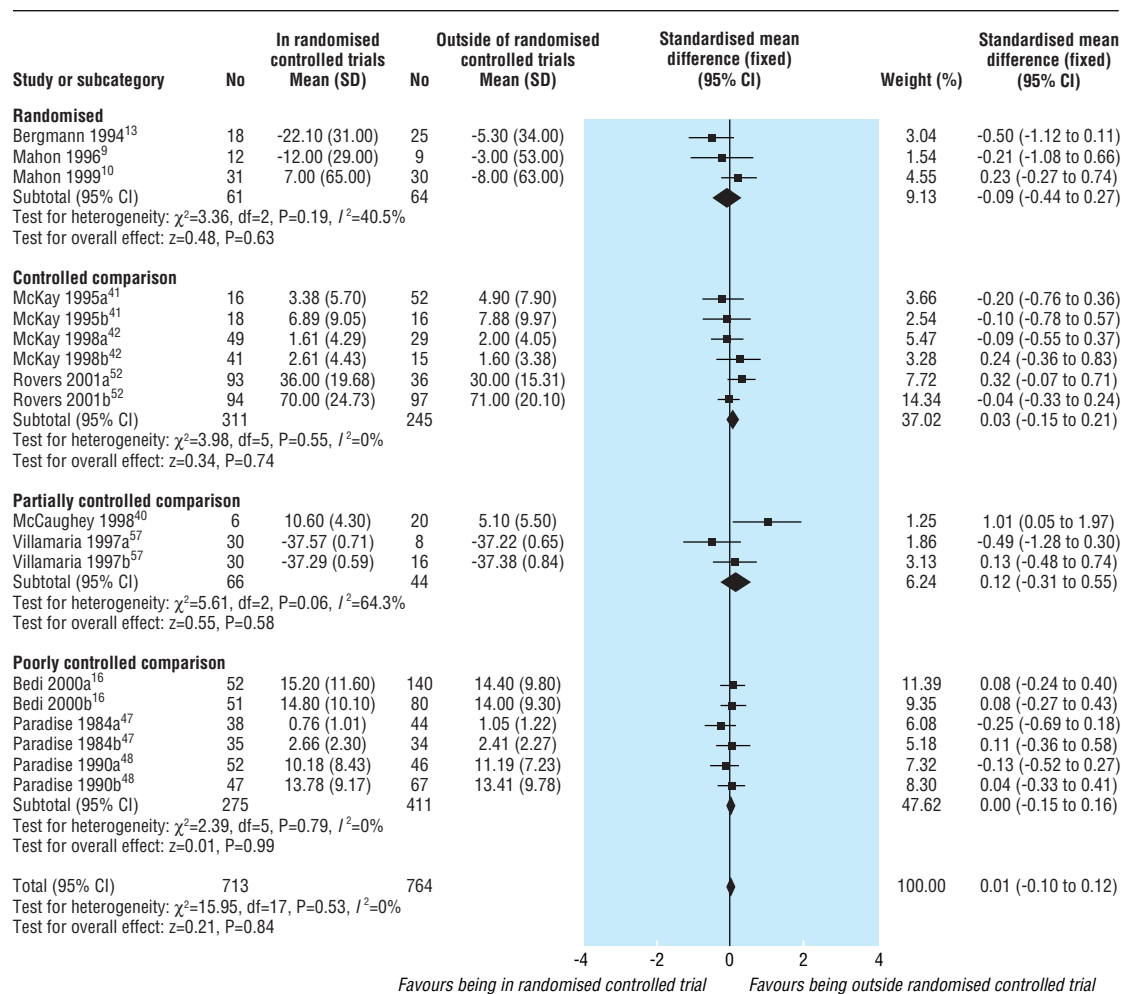
A table giving the evidence profile of results is on bmj.com



This is the abridged version; the full version is on bmj.com



**Fig 1** Results of dichotomous main outcomes in participants of randomised controlled trials and comparable non-participants who received the same or similar treatment



**Fig 2** Results of continuous main outcomes in participants of randomised controlled trials and comparable non-participants who received the same or similar treatment

no statistically significant ( $P < 0.10$ ) heterogeneity was found among similar comparisons. We constructed a funnel plot to explore the possibility of publication bias.

## Results

Overall, 55 studies, totalling 91 comparisons, met our inclusion criteria (see [bmj.com](http://bmj.com)). Forty one studies are still awaiting assessment.

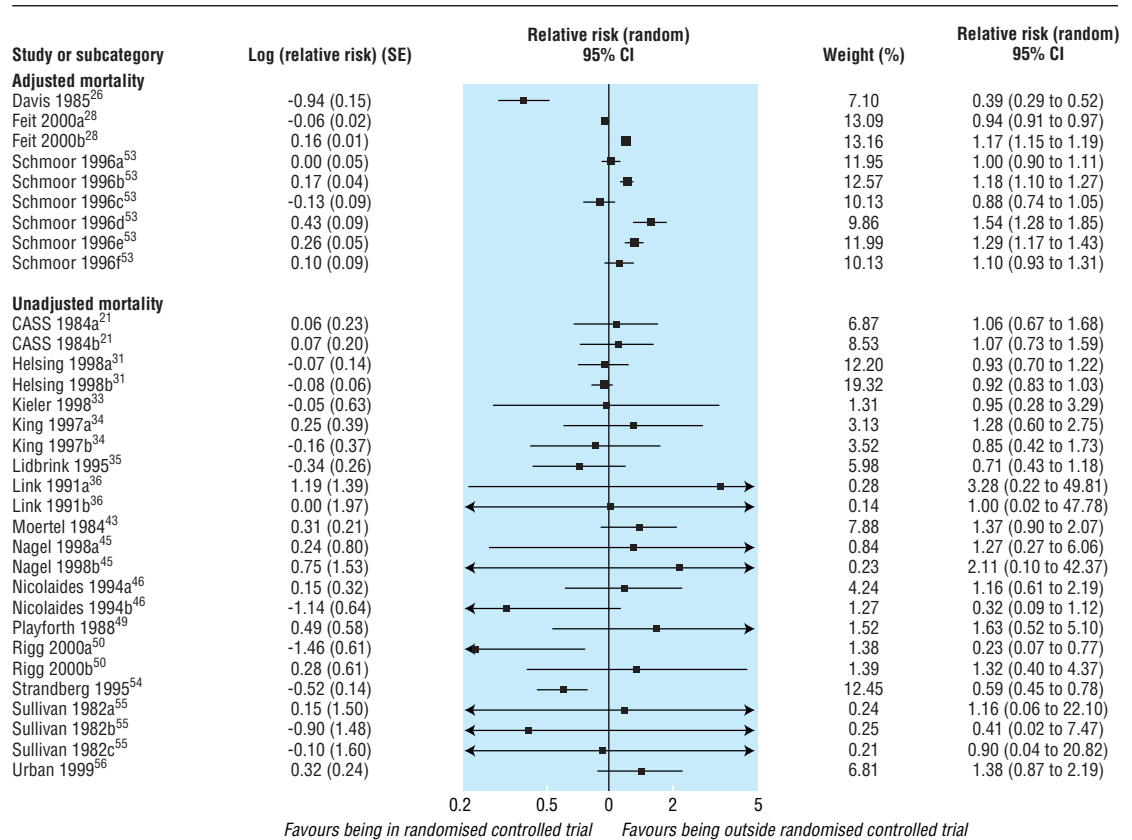
We identified five RCTs (six comparisons) in which patients were randomised according to whether they had the option to participate. These studies provided limited data because of their small sample sizes and the nature of the questions considered. Two studies randomised 82 patients to “n of 1 trials” compared with standard practice.<sup>7, 8</sup> One study (60 patients) measured spontaneously self reported side effects in patients who had or had not been informed that they were in an RCT.<sup>9</sup> One study (227 patients) reported satisfaction among patients randomised to an RCT compared with patients randomised to a patient preference trial in which they had a choice of treatment.<sup>10</sup> Another study (43 patients) reported pain reduction among patients randomised to an RCT compared with those who were not invited to

participate.<sup>11</sup> None of these studies found significant differences in outcomes between patients treated in or outside RCTs.

We identified 50 cohort studies (85 comparisons) totalling 30 862 patients participating in RCTs compared with 20 246 patients treated outside RCTs.<sup>w1-w50</sup> Seventy comparisons comprised dichotomous outcomes, of which 12 reported adjusted estimates, and 15 comparisons comprised continuous outcomes.

We found significant heterogeneity ( $I^2 = 89.0\%$ ) among the results of comparisons with dichotomous main outcomes (fig 1). Of these 73 comparisons, 59 reported no significant differences between outcomes for patients treated in RCTs and those receiving similar treatments outside RCTs, 10 reported significantly better outcomes for patients treated in RCTs, and four reported significantly worse outcomes for patients treated in RCTs.

Figure 2 shows the results of the 18 comparisons with continuous main outcomes. We found no significant heterogeneity ( $I^2 = 0\%$ ). The pooled estimate found no differences in outcomes for patients treated in and outside RCTs (standardised mean difference 0.01, 95% confidence interval  $-0.10$  to  $0.12$ ).



**Fig 3** Comparison of mortality between participants of randomised controlled trials and comparable non-participants who received the same or similar treatment

In 17 studies (32 comparisons) with data on mortality (fig 3), we found significant heterogeneity ( $I^2 = 88.8\%$ ). In 24 of the 32 comparisons we found no significant difference in mortality. Four comparisons reported a significant lower risk of mortality for patients treated in RCTs and four comparisons reported a significantly higher risk of mortality.

Separate subgroup analyses could not explain the observed heterogeneity by the different types of eligible non-participants, treatments, clinical specialties, or study quality (selection bias, detection bias, and exclusion bias). See [bmj.com](http://bmj.com) for a summary of the studies included in the sensitivity analysis.

A funnel plot of the dichotomous comparisons showed no asymmetry (see [bmj.com](http://bmj.com)), indicating a low risk of publication bias.

## Discussion

Our systematic review found no strong evidence of a harmful or beneficial trial effect of participating in randomised controlled trials (RCTs). The five included RCTs provided limited evidence because of their small sample size and the nature of the question considered, but showed that it is possible to consider questions about the effects of participating in RCTs by using randomised designs. Our interpretation of the 50 non-randomised cohort studies was limited by the quality and size of the comparisons and the wide variations in participants, clinical interventions, and outcomes. Most of the 85 non-randomised cohort comparisons found no statistically significant differ-

ences, although 10 reported better outcomes for patients in RCTs and four reported better outcomes for patients outside of RCTs.

Previous reviews that considered a less precise question than the one we evaluated drew varied conclusions. Our review differs from these reviews in several ways, including the scope and comprehensiveness of our search, our method of analysis, and the question we asked, which controlled for differences in the effects of different interventions and differences between participants and non-participants. Our results are based mainly on comparisons of cohorts and are subject to the usual uncertainty associated with observational studies.<sup>12</sup> Additionally, we could not explain the significant heterogeneity between studies. Other relevant studies apart from those included in this review may exist, as indicated by the number of studies awaiting assessment and the difficulty encountered in searching for this type of study. As we did not find evidence of publication bias, and it is unlikely that the studies that we failed to identify would provide strong evidence of either harmful or beneficial effects.

An important corollary of this finding is that it counters suggestions that the results of RCTs cannot be applied to usual clinical practice, because most of the studies found no significant difference in outcomes for participants of RCTs compared with comparable non-participants who received similar treatment.

See [bmj.com](http://bmj.com) for acknowledgments  
Contributors: See [bmj.com](http://bmj.com)

### What is already known on this topic

Some people believe that participation in a randomised controlled trial (RCT) increases a patient's risk of a bad outcome

Some people claim that the results of RCTs are not applicable to usual clinical practice

### What this study adds

Participants in RCTs had similar outcomes to comparable patients who received the same or similar treatment outside the trial

The results of RCTs are therefore applicable to comparable patients in usual clinical practice

Funding: Norwegian Health Services Research Centre, McMaster University, and the Nuffield Trust.

Competing interests: None declared.

Ethical approval: Not required.

- 1 Stiller CA. Centralised treatment, entry to trials and survival. *Br J Cancer* 1994;70:352-62.
- 2 Braunholtz DA, Edwards SJL, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect." *J Clin Epidemiol* 2001;54:217-24.

- 3 Emergency Care Research Institute 2002. Patients' reasons for participation in clinical trials and effect of trial participation on patient outcomes. [www.ecri.org/Patient\\_Information/Patient\\_Reference\\_Guide/evidence.pdf](http://www.ecri.org/Patient_Information/Patient_Reference_Guide/evidence.pdf) (accessed Nov 2004).
- 4 Peppercorn JM, Weeks JC, Cook EFC, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet* 2004;363:263-70.
- 5 Rothwell PM. External validity of randomised controlled trials: "To whom do the results of this trial apply?" *Lancet* 2005;365:82-93.
- 6 Higgins JP, Thompson SG. Quantifying heterogeneity in meta-analysis. *Stat Med* 2002;21:1539-58.
- 7 Mahon J, Laupacis A, Donner A, Wood T. Randomised study of n of 1 trials versus standard practice. *BMJ* 1996;312:1069-74.
- 8 Mahon JL, Laupacis A, Hodder RV, McKim DA, Paterson NAM, Wood TE, et al. Theophylline for irreversible chronic airflow limitation. A randomized study comparing n of 1 trials to standard practice. *Chest* 1999;115:38-48.
- 9 Dahan R, Caulin C, Figea L, Kanis JA, Caulin F, Segrestaa JM. Does informed consent influence therapeutic outcome? A clinical trial of the hypnotic activity of placebo in patients admitted to hospital. *BMJ* 1986;293:363-4.
- 10 Cooper KG, Grant AM, Garratt AM. The impact of using a partially randomised patient preference design when evaluating alternative managements for heavy menstrual bleeding. *Br J Obstet Gynaecol* 1997;104:1367-73.
- 11 Bergmann JF, Chassany O, Gandiol J, Deblois P, Kanis JA, Segrestaa JM, et al. A randomised clinical trial of the effect of informed consent on the analgesic activity of placebo and naproxen in cancer pain. *Clin Trials Metaanal* 1994;29:41-7.
- 12 Kunz R, Vist G, Oxman AD. Randomisation to protect against selection bias in healthcare trials (Cochrane methodology review). In: *Cochrane Library*. Issue 4. Oxford: Update Software, 2002.

(Accepted 31 March 2005)

doi 10.1136/bmj.38447.490463.8F

## Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey

R Brian Haynes, K Ann McKibbin, Nancy L Wilczynski, Stephen D Walter, Stephen R Werre for the Hedges Team

### Abstract

**Objective** To develop and test optimal Medline search strategies for retrieving sound clinical studies on prevention or treatment of health disorders.

**Design** Analytical survey.

**Data sources** 161 clinical journals indexed in Medline for the year 2000.

**Main outcome measures** Sensitivity, specificity, precision, and accuracy of 4862 unique terms in 18 404 combinations.

**Results** Only 1587 (24.2%) of 6568 articles on treatment met criteria for testing clinical interventions. Combinations of search terms reached peak sensitivities of 99.3% (95% confidence interval 98.7% to 99.8%) at a specificity of 70.4% (69.8% to 70.9%). Compared with best single terms, best multiple terms increased sensitivity for sound studies by 4.1% (absolute increase), but with substantial loss of specificity (absolute difference 23.7%) when sensitivity was maximised. When terms were combined to maximise specificity, 97.4% (97.3% to 97.6%) was achieved, about the same as that achieved by the best single term (97.6%, 97.4% to 97.7%). The strategies newly reported in this paper outperformed other

validated search strategies except for two strategies that had slightly higher specificity (98.1% and 97.6% v 97.4%) but lower sensitivity (42.0% and 92.8% v 93.1%).

**Conclusion** New empirical search strategies have been validated to optimise retrieval of articles from Medline reporting high quality clinical studies on prevention or treatment of health disorders.

### Introduction

If large bibliographic databases such as Medline are to be helpful to clinical users, clinicians must be able to retrieve articles that are scientifically sound and directly relevant to the health problem they are trying to solve, yet few clinicians are trained in search techniques. Search filters ("hedges") can improve the retrieval of clinically relevant and scientifically sound study reports from Medline and similar bibliographic databases.<sup>1-6</sup> Hedges can be created with appropriate disease content terms combined ("ANDed") with

Editorial by Sanders and Del Mar

Health Information Research Unit, McMaster University, Hamilton, ON, Canada L8N 3Z5

R Brian Haynes  
chief

Stephen R Werre  
research associate

School of Graduate Studies, McMaster University  
Nancy L Wilczynski  
doctoral candidate

Department of Clinical Epidemiology and Biostatistics, McMaster University  
Stephen D Walter  
professor

continued over



This is the abridged version of an article that was posted on [bmj.com](http://bmj.com) on 13 May 2005: <http://bmj.com/cgi/doi/10.1136/bmj.38446.498542.8F>

BMJ 2005;330:1179-82