

- ¹² Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults: meta-analysis of individual patient data. *Lancet* 1997;**350**:1647–54.
- ¹³ Advanced Ovarian Cancer Trialists' Group. Chemotherapy in advanced ovarian cancer: four systematic meta-analyses of individual patient data from 37 randomized trials. *Br J Cancer* 1998;**78**:1479–87.
- ¹⁴ Arnott SJ, Duncan W, Gignoux M *et al*. Preoperative radiotherapy in esophageal carcinoma: a meta-analysis using individual patient data (Oesophageal Cancer Collaborative Group). *Int J Radiat Oncol Biol Phys* 1998;**41**:579–83.
- ¹⁵ PORT Meta-analysis Trialists Group. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. *Lancet* 1998;**352**:257–63.
- ¹⁶ Glioma Meta-analysis Trialists (GMT) Group. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. *Lancet* 2002;**359**:1011–18.
- ¹⁷ Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: An overview of the randomized trials. *Prog Cardiovasc Dis* 1985;**27**:335–71.
- ¹⁸ Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557–60.
- ¹⁹ Machin D, Stenning SP, Parmar MKB *et al*. Thirty years of Medical Research Council trials in solid tumours. *Clin Oncol* 1997;**9**:100–14.
- ²⁰ Vale C, Stewart L. What can we learn from a prospective trials register? Trends and changes in randomised controlled trials in cancer in the UK. 11th Cochrane Colloquium, Barcelona 2003:P-65,50.
- ²¹ Altman DG, Doré CJ. Randomisation and baseline comparisons in clinical trials. *Lancet* 1990;**335**:149–53.
- ²² Schulz KF, Chalmers I, Hayes RJ, Altman DA. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**:408–12.
- ²³ Schulz KF, Grimes DA, Altman DG, Hayes RJ. Blinding and exclusions after allocation in randomised controlled trials: survey of published parallel group trials in obstetrics and gynaecology. *BMJ* 1996;**312**:742–44.
- ²⁴ Begg C, Cho M, Eastwood S *et al*. Improving the quality of reporting of randomised controlled trials. *JAMA* 1996;**276**:637–39.
- ²⁵ Hollis S, Campbell F. What is meant by intention-to-treat analysis? Survey of published randomised controlled trials. *BMJ* 1999;**319**:670–74.
- ²⁶ Moher D, Schulz KF, Altman Douglas, for the CONSORT Group. The CONSORT Statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001;**285**:1987–91.
- ²⁷ Egger M, Jüni P, Bartlett C, for the CONSORT Group. Value of flow diagrams in reports of randomized controlled trials. *JAMA* 2001;**285**:1996–99.

Commentary: Empirical evidence of attrition bias in clinical trials

Peter Jüni^{1,2} and Matthias Egger^{1,2*}

Excluding the 5 patients who died and the 10 who had permanent postoperative deficits, there remained 79 patients available for follow-up and at risk of subsequent persistent stroke and death.

This is how, in 1970, Fields and colleagues analysed the data from the Joint Study of Extracranial Arterial Occlusion, which had randomly allocated patients with bilateral carotid stenosis to carotid endarterectomy or medical treatment.¹ Among the patients who had survived surgery and were 'available for follow-up', a 26% reduction in the risk of recurrent transient

ischaemic attacks, stroke, or death was observed, compared with patients who had received conventional treatment ($P = 0.02$). Around the same time Bradford Hill, in the ninth edition of his *Principles of Medical Statistics*, pointed out that excluding patients after 'admission to the treated or control group' may affect the validity of clinical trials and that 'unless the losses are very few and therefore unimportant, we may inevitably have to keep such patients in the comparison and thus measure the 'intention to treat' in a given way, rather than the actual treatment'.² Indeed, when several years later Sackett and Gent³ re-analysed the study according to this intention to treat principle the results were less convincing: the reduction in the risk was 17% ($P = 0.09$) (Figure 1).

In more recent years, the debate has shifted from anecdotal evidence of bias in single trials to more sophisticated 'meta-epidemiological' research, based on many trials and meta-analyses.⁴ Schulz and colleagues⁵ pioneered this approach when they assessed the methodological quality of 250

¹ Department of Social and Preventive Medicine, University of Berne, Finkenhubelweg 11, CH-3012 Bern, Switzerland.

² MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol BS8 2PR, UK.

* Corresponding author. Department of Social and Preventive Medicine, University of Berne, Finkenhubelweg 11, CH-3012 Bern, Switzerland. E-mail: egger@ispm.unibe.ch

trials from 33 meta-analyses from the Cochrane Pregnancy and Childbirth Database and examined the association between dimensions of trial quality and estimated treatment effects. Compared with trials in which authors reported adequately concealed treatment allocation, failure to prevent foreknowledge of treatment allocation was associated, on average, with an exaggeration of treatment effects by 30–40%. Trials that were not double-blind also yielded larger effects. These bias effects were subsequently confirmed in several other studies.⁶ There is thus convincing empirical evidence that trials of lower methodological quality that are susceptible to selection bias, performance bias, or detection bias produce, on average, larger treatment effects than trials of higher quality that avoided or minimized such biases.

What about attrition bias? So far three studies examined the influence of this type of bias, which, as the example of the Joint Study of Extracranial Arterial Occlusion shows can be of great importance. Schulz *et al.* compared trials that reported exclusions with trials that either explicitly reported no exclusions or gave the impression that no exclusions had taken place.⁵ The other two studies assessed the quality of reporting, rather than methodological quality. Kjaergard *et al.* compared trials that reported adequately on attrition (independent of whether exclusions occurred) to trials with inadequate reporting.⁷ Similarly, Balk *et al.*⁸ assessed whether dropouts had been recorded (either explicitly or by reporting the number enrolled and the number evaluated). Schulz *et al.* found little difference in effect estimates whereas the Kjaergard and Balk studies found trends in opposite directions. The methods used to assess attrition were unsatisfactory in all cases, because reports often omit important methodological details.⁶ In particular, it is problematic to deduce that a trial was analysed according to the intention to treat principle if no exclusions are reported.⁹ And it is equally problematic to assume that an analysis described as intent to treat did in fact include all patients, according to random allocation.¹⁰

The elegant study by Tierney and Stewart¹¹ for the first time directly assesses the impact of attrition bias. Stewart and colleagues have co-ordinated individual patient data meta-analyses of clinical trials in oncology for many years and now present a comparison of the results from their analyses, which invariably followed the intention to treat principle with those done by the original investigators, which often excluded some or many patients. The results confirmed what methodologists had been suspecting for some time: pooled analyses of trials with patient exclusions showed more beneficial effects of the experimental treatment than analyses based on all or most patients randomized. It therefore seems likely that the earlier studies^{5,7,8} either suffered from measurement error due to incomplete reporting or assessed an inappropriate proxy measure, reporting quality.¹² The effects of attrition bias in these meta-analyses were modest in most cases, but, as Tierney and Stewart point out, they may well underestimate the extent of bias in other situations. Investigators who participate in collaborative meta-analyses of cancer trials are probably methodologically more astute and not representative of all

investigators in this field, and certainly not representative of trialists in general. Of note, although the bias will in general lead to exaggerated treatment effects, Stewart and Tierney also show that it can go in either direction, and predicting its effect in a specific situation will be difficult.

Individual patient data meta-analyses have been described as the 'yardstick' against which other forms of systematic review and meta-analysis should be measured.¹³ Tierney and Stewart's paper is another example of the power of such analyses, which in a number of cases have produced definitive answers that might not have been obtained in any other way.¹⁴ Their approach should be applied more widely to further develop our understanding of the mechanisms that introduce bias in clinical trial research.

References

- Fields WS, Maslenikov V, Meyer JS, Hass WK, Remington RD, Macdonald M. Joint study of extracranial arterial occlusion. V. Progress report of prognosis following surgery or nonsurgical treatment for transient cerebral ischemic attacks and cervical carotid artery lesions. *JAMA* 1970;**211**:1993–2003.
- Bradford Hill A. *Principles of Medical Statistics*, 9th edn. London: The Lancet Limited, 1971.
- Sackett DL, Gent M. Controversy in counting and attributing events in clinical trials. *N Engl J Med* 1979;**301**:1410–12.
- Sterne JAC, Jüni P, Schulz KF, Altman DG, Bartlett C, Egger M. Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. *Stat Med* 2002;**21**:1513–24.
- Schulz KF, Chalmers I, Hayes RJ, Altman D. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**:408–12.
- Jüni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. *BMJ* 2001;**323**:42–46.
- Kjaergard LL, Villumsen J, Gluud C. Reported methodological quality and discrepancies between large and small randomized trials in meta-analyses. *Ann Intern Med* 2001;**135**:982–89.
- Balk EM, Bonis PA, Moskowitz H *et al.* Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. *JAMA* 2002;**287**:2973–82.
- Schulz KF, Grimes DA. Sample size slippages in randomised trials: exclusions and the lost and wayward. *Lancet* 2002;**359**:781–85.
- Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* 1999;**319**:670–74.
- Tierney JF, Stewart LA. Investigating patient exclusion bias in meta-analysis. *Int J Epidemiol* 2005;**34**:79–87.
- Huwiler-Müntener K, Jüni P, Junker C, Egger M. Quality of reporting of randomized trials as a measure of methodological quality. *JAMA* 2002;**287**:2801–04.
- Chalmers I. The Cochrane Collaboration: preparing, maintaining and disseminating systematic reviews of the effects of health care. *Ann NY Acad Sci* 1993;**703**:156–63.
- Clarke MJ, Stewart LA. Obtaining individual patient data from randomised controlled trials. In: Egger M, Davey Smith G, Altman DG (eds). *Systematic Reviews in Health Care: Meta-analysis in Context*, 2nd edn. London: BMJ Books, 2000.