CURRENT OPINION

Drug Safety 2002; 25 (2): 77-84
0114-5916/02/0002-0077/$25.00/0

Improving Safety Reporting from Randomised Trials

John P.A. Ioannidis[1,2] and *Joseph Lau*[2]

1 Clinical Trials and Evidence-Based Medicine Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece
2 Division of Clinical Care Research, New England Medical Center, and the Department of Medicine, Tufts University School of Medicine, Boston, USA

Abstract

Randomised clinical trials offer a unique opportunity for capturing safety information under a controlled setting that minimises biases in the comparison of different therapeutic options. Nevertheless, empirical evidence across diverse medical fields suggests that the reporting of safety information in clinical trials is largely neglected and receives less attention compared with efficacy outcomes. An analysis of 192 randomised trials has shown that reasons for withdrawals due to toxicity were specified per study arm in only 46% of the trial reports. Adequate reporting of clinical adverse effects and laboratory-determined toxicity occurred in only 39 and 29% of the trials, respectively, even with lenient definitions of what constitutes adequate reporting. The use of standardised scales for adverse effects is a prerequisite for improved reporting on safety in randomised trials. Safety data need to be collected and analysed in a systematic fashion and active surveillance for toxicity during the conduct of a randomised trial is preferable to passive surveillance. Standardised reporting of safety data does not necessarily require extensive space to accomplish. It is essential to provide numerical data per study arm on each type of adverse effect along with a categorisation of the severity of the adverse effects with an emphasis on severe and life-threatening reactions. The severity grading must be referred to well-known standardised scales and new scales need to be carefully defined. Information on withdrawals due to toxicity is also important to report, along with the specific reasons leading to discontinuation. Tabulation of information may be helpful and rare or not previously reported adverse effects should be described in detail. The availability of newer options such as electronic publication, publication of raw databases, large database research, meta-analytic approaches, and prospective registration of clinical trials and of their databases may further improve the safety insights we can gain from randomised clinical trials.

Randomised clinical trials provide an opportunity for collecting in a systematic way, analysing in a controlled setting, and presenting in usable form information on the adverse effects of medical interventions. Medical decision making is increasingly based on individualising medical management based on balancing benefits against risks.[1] Both physicians and patients have increasing demands to know in more detail about the potential adverse effects of interventions offered to them. A recent survey[2] showed that 76.2% of outpatients desired to be told of every single possible adverse effect of treatment. However, are safety data available in such detail when randomised trials are published?

1. Current Status of Safety Reporting in Randomised Trials

In a pilot project,[3] we examined the reports of 60 randomised trials in the domain of antiretroviral therapy. Reasons and numbers for withdrawals due to toxicity per study arm were given only in 23 trials (38%). Only 19 reports (32%) gave the number of patients with severe or life-threatening toxicity per study arm for at least two types of clinical adverse events. 37 reports (62%) provided the number of patients per study arm who had severe or life-threatening toxicity for at least two types of laboratory adverse events. We considered such information as comprising a minimum for adequate reporting of clinical adverse events and laboratory-defined toxicity, respectively.

We extended these observations by evaluating 192 randomised trials involving over 100 patients each covering 7 diverse medical areas.[4] Clinical adverse effects and laboratory-determined toxicity were adequately defined in only 39 and 29% of trial reports, respectively. Slightly less than half of the trials (46%) stated the frequency of specific reasons for discontinuation of study treatment due to toxicity. The adequacy of reporting varied across each of the 7 medical areas (figure 1). The median space devoted to safety was only 0.3 pages, a similar space as that devoted to contributor names and affiliations ($p = 0.16$). Trials that reported statistically significant results for efficacy measures seemed to devote significantly less space for safety, suggesting that safety is more neglected when there is good news about efficacy. For obvious reasons, emphasis on safety improved in dose-comparison studies.

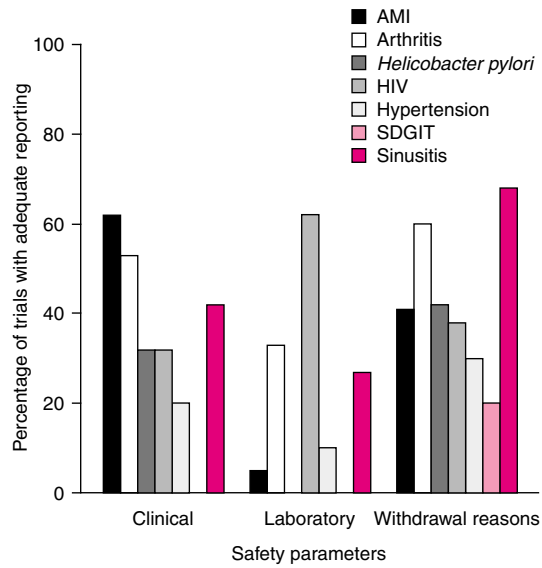

Fig. 1. Percentage of randomised clinical trials involving at least 100 patients and with at least 50 patients per study arm that have adequate reporting for clinical adverse events, laboratory-defined toxicity and reasons for withdrawals due to toxicity. Data are provided for 7 different medical areas.[4] **AMI** = acute myocardial infarction; **HIV** = human immunodeficiency virus; **SDGIT** = selective decontamination of the gastrointestinal tract.

Similar observations have started accumulating from other fields as well.[5] Some medical fields may be better than others depending on the emphasis that adverse effects have traditionally received and the availability and widespread adoption of standardised scales for safety reporting.

Complete reporting of safety data in a standardised format is even more important when toxicity data are to be synthesised across several trials, as in meta-analyses.[6,7] The combination of data across several trials on the same topic increases statistical power, decreases the uncertainty about the examined treatment effects and can help quan-

tify and possibly also explain the observed heterogeneity in the rates of adverse events between the various studies. Theoretically, meta-analysis of randomised trials would be an excellent method for addressing relatively uncommon, yet serious, potential adverse effects, since individual studies might be underpowered for evaluating their association with a given treatment, or would leave large uncertainty about the magnitude of the association. Nevertheless, early attempts to implement meta-analyses of safety data have acknowledged important difficulties stemming from inadequately reported data.[8] More recently, we have seen several examples of meta-analyses focusing on safety outcomes.[9-13] However, in the majority of these cases, the toxicity of the evaluated intervention was considered upfront to be a major end-point of the individual randomised trials. The situation is still difficult when toxicity does not have such a prominent role in the design of randomised trials.[13]

Two recent empirical studies have shown that most systematic reviews and meta-analyses are deficient in listing, let alone quantitatively analysing, toxicity information. One empirical evaluation of published systematic reviews found that even in 1996 to 1999, there were 819 systematic reviews with efficacy outcomes, 278 mentioned safety without evaluating it, 34 evaluated safety outcomes but these were not the main focus, and only in 44 systematic reviews safety was a major focus.[14] Another empirical evaluation found similar lack of attention on safety, when systematic reviews from the Cochrane database were examined.[15] The lack of standardised information from randomised trial reports is probably a key reason for this neglect.

2. Approaches to Improve Safety Reporting

Given the obvious deficiencies in the field, there is considerable room for improving the reporting and use of safety information in randomised trials. We will discuss improvements in standardised scales for adverse effects, collection of adverse effects data, standardised reporting, availability of raw databases, and special aspects when dealing with latent, unrecognised and very uncommon, but serious, adverse effects in the randomised trial setting.

2.1 Standardised Scales for Adverse Effects

In order to allow meaningful reporting and interpretation of adverse events, the information should be categorised and coded according to validated scales. Using a common, widely accepted scale has the advantage that information can then be compared and synthesised across different studies. Several scales for reporting adverse events have enjoyed wide popularity, including the National Cancer Institute (NCI)[16] and WHO scales.[17] Such scales are typically all-inclusive and they capture information per organ system. They include a severity/intensity dimension for categorising adverse events (e.g. mild/moderate/severe/life-threatening adverse event).

While the use of standardised scales improves the comparability of information within the same field, sometimes it may be difficult or inappropriate to use the same scale in very different fields. The popularity of a scale may not guarantee its applicability in special circumstances and some scales may be outdated for specific applications. Customised scales may be more applicable for specific questions. For example, if the clinical benefit pertains to a soft outcome, even mild toxicity may be worrisome, while moderate toxicity may be prohibitive for the adoption of the proposed intervention. In this case, more detailed categorisation within the 'mild' and 'moderate' categories may be indicated. For example, safety scales for interventions to prevent or treat the common cold, need a different focus on the severity scale than interventions used to treat a lethal malignancy. In addition, other composite parameters of efficacy and safety may need to be considered, such as measurements of quality of life which extend beyond the scope of this paper.[18]

While some medical fields have used only one or a few scales for assessing toxicity, others are still using a very large number of different scales or are still searching for an optimal scale. This may create

difficulties in the comparability of reported toxicity data, as has been described in rheumatology.[19] In other fields, the diversity can be extreme. An evaluation[20] of 2000 randomised trials in schizophrenia found that 431 of them used at least one adverse effect scale for capturing and reporting toxicity and a total of 67 different toxicity scales had been used. There were 640 different scales utilised when all safety, efficacy and global measures were considered, thus creating havoc for interpretation.

2.2 Collection of Safety Data to be Reported in Clinical Trials

The appropriate collection of information on adverse events is a prerequisite for adequate reporting. Even when appropriate standardised scales are used, the collected information may be qualitatively and quantitatively very different depending on how adverse events are captured. We will discuss some key issues, but for a more detailed discussion of the subject and more detailed guidance on how to collect and interpret safety data, the reader is referred to more extensive relevant literature.[21,22]

Active surveillance for adverse effects provides more reliable estimates of the frequency of adverse reactions than passive surveillance.[23] Active surveillance is fairly straightforward for laboratory toxicity, when blood and other tests are performed at time intervals specified by the study protocol. Ideally, patients in each of the study arms should have exactly the same schedule for laboratory testing. Sometimes this is not feasible, since patients in the experimental arm may undergo more laboratory tests, leading to diagnosis bias, especially in unblinded trials. Other caveats about the collection and analysis of laboratory toxicity data, such as the use of reference ranges, the one-parameter-at-a-time approach and the exploratory nature of laboratory data in clinical trials are discussed in more detail by Chuang-Stein.[24]

Active surveillance may be more difficult to standardise for clinical adverse events. Even with active surveillance, retrospective questioning of the patient may not yield the correct or total information. Patient diaries may be difficult to standardise. When extensive questionnaires are used, they may be difficult and time consuming to implement in the busy clinic setting. Observer bias may also interfere in determining what constitutes an adverse event and what severity is to be recorded. Different health providers and different clinical sites may differ in the amount of reported and coded information. Furthermore, active surveillance with participation of the health provider may be misleading, if the provider is biased in favour of a new medication, especially in unblinded trials and in trials without proper allocation concealment.

Finally, even with careful, active surveillance of adverse effects, the occurrence and reporting of adverse effects may also be affected by characteristics of the study design or tradition. In an evaluation of 25 placebo-controlled and 33 comparative trials of NSAIDs,[25] withdrawals due to adverse effects were more common in trials without a placebo group [odds ratio 1.5, 95% confidence interval (CI), 1.1 to 1.9]. Similarly, adverse effects relating to skin (odds ratio 4.2, 95% CI, 1.7 to 9.9), gastrointestinal (odds ratio 1.7, 95% CI, 1.3 to 2.0), and other types of toxicity (odds ratio 5.3, 95% CI, 3.8 to 7.4) were more common when there was no placebo arm in a trial. The inclusion of a placebo arm probably changes how patients rate the toxicity of a drug. In another study, Hayashi and Walker[26] compared 27 US and 22 Japanese trial reports of diclofenac or simvastatin. Japanese reports offered more detailed data, but usually included only those adverse effects which attending clinicians attributed to the study drug. US reports reported far less detail, but included adverse effects regardless of attribution to the study drug or not. While two-thirds of the US reports reported significant differences in adverse effects between the compared arms, this was reported in only one third of the Japanese reports.

2.3 Standardised Reporting

In our experience some of the common errors made while reporting safety information are the following:

1. Not reporting any safety data at all. Occasionally, a trial may refer to an additional manuscript that will examine safety outcomes, however in most cases, such trials simply ignore safety completely.
2. Making only vague statements such as 'the medication was quite well tolerated' or 'the observed adverse effects were ordinary and anticipated'.
3. Reporting safety data without specifying a breakdown of events per study arm. Then, regardless of the detail of the provided information, the data cannot be ascribed to a specific intervention.
4. Reporting numbers of adverse effects, but lumping different kinds of adverse effects under broad categories that cannot be translated into clinically useful, identifiable information (e.g. 'x patients had severe adverse events' or 'y subjects had gastrointestinal adverse effects').
5. Reporting adverse effects without providing information on their severity or lumping together numbers for different severity levels. Thus, a statement that '30 patients had diarrhoea' is almost useless unless there is a description of the severity. Typically, it is most important to know the number of patients who have severe or life-threatening adverse effects. A statement that '30 patients had moderate or severe or life-threatening diarrhoea' is also largely confusing.
6. Giving p-values for the comparison of specific adverse events between the study arms without reporting actual numbers per severity level. This information (e.g. 'severe diarrhoea was more common in the experimental group, $p = 0.04$') cannot be interpreted for clinical purposes. Actually, hypothesis testing for safety data is problematic. Given the large diversity of adverse effects, statistical significance may sometimes be reached by chance alone due to multiple comparisons. Conversely, most randomised trials are not adequately powered for detecting significant differences for most adverse effects, except very common ones.
7. Providing information on only the most common or only a few types of adverse events. Then it is not possible to know whether other adverse events did not occur at all, or were simply neglected in the reporting.
8. Failing to provide information on adverse events that led to discontinuation of study treatment. Withdrawals may often occur even in patients with moderate or mild adverse effects, while some patients who experience severe toxicity may persevere on the study treatment. Therefore, withdrawals provide an independent, complementary measure of tolerance that is important for the implementation of a treatment in clinical practice. Tolerance may be different in a study setting than in real practice, but a randomised trial offers a unique controlled background. This is even more important if the trial is double-blind and with adequate allocation concealment. Similar to information on adverse events, information on withdrawals needs to be provided per study arm and per type of reason for withdrawal.
9. Over-interpreting and over-analysing safety information by providing data on subgroups of patients without providing the data for the total population. While predictive models for safety outcomes need to be encouraged, such efforts should not replace the need to offer the aggregate data per arm. Subgroup analyses and predictive models may then offer additional, although largely exploratory, information.
10. Over-interpreting the absence of adverse effects, especially when the sample size is small. The upper boundary of the 95% confidence interval for the occurrence of a specific adverse effect is $3/n$ when the adverse effect has not been observed among n patients. Thus for $n = 10$, the upper boundary is approximately 30%, and for $n = 50$, the upper boundary is still 6%, a very impressive percentage if the adverse effect leads to major morbidity.
11. Failing to define the scale(s) used for categorising the severity of the reported safety data. If a widely known, standardised scale is employed, this should be clearly stated. Important modifications should be adequately described. If a new or relatively unknown scale is used, more explanation is required in the Methods section of the paper. Using an unknown, nonvalidated scale is problematic.
12. Reporting events without proper data on the observational unit. For longitudinal studies, it is

important to state not only the number of adverse effects, but also the timeframe within which they occur. Their distribution over time may also provide useful information, especially if the incidence of a specific adverse event differs in the early phase of treatment versus late follow-up. In many cases, it does not suffice to provide simply the total number of patients, but information should also be given on the number of patients at risk at various time intervals and/or the person-years of follow-up. Incidence estimates may be more appropriate than simple proportions for analysing longitudinal data.

Attention to these potential problems should help improve safety reporting. It should be noted that at present the available standards for reporting of clinical trials, such as the Consolidated Standards of Reporting Clinical Trials (CONSORT) statement,[27-29] do not include very detailed guidance on how to report adverse effects. However, safety reporting may be one of the next priority targets of the CONSORT team in the near future.

Finally, information about safety also includes characteristics of the study design that have an impact on the occurrence of adverse effects, i.e. whether certain subgroups of patients were ineligible for participation based on the fear of toxicity. A recent survey[30] found that only 57% of the examined randomised trial reports stated safety-related eligibility criteria.

2.4 Availability of Raw Databases, Trial Registration and Long-Term Toxicity Reporting

It is possible to make use of the advances in electronic media communication in order to improve the availability of detailed standardised safety information from randomised trials. Electronic publication should allow the raw data from any randomised trial to be posted on the World Wide Web.[31,32] According to good clinical practice standards, the databases of randomised trials should be available for 15 years, but this has been the exception rather than the rule. Hopefully, electronic data availability should largely bypass this problem.[32] Availability of detailed safety databases may allow secondary analyses or meta-analyses of safety outcomes to be performed with higher accuracy and compatibility of the outcomes among various combined studies. In this regard, it is essential to ensure that all randomised trials are equally retrievable. Publication bias and time lag bias, the lack or delay of publication and disappearance of studies with 'negative' results is a threat to evidence-based medicine.[33,34] The effects of publication bias are clear when efficacy outcomes are involved, but we have no good empirical evidence on what its effect may be on the synthesis of safety outcomes. Registration of clinical trials may offer a solution to this problem. Retrospective registration, such as conducted by the Cochrane Controlled Trials Registry[35] is one approach, but prospective registration is likely to be more efficient. Although this concept has been proposed for over 15 years now,[36] it is only recently that serious efforts have been made to register clinical experimental research prospectively.[37]

Another evolving concept is the long-term collection and reporting of information on toxicity from randomised trials long after these trials have completed their efficacy evaluations. This is important for some fields where the most important toxicities are likely to occur many years after the evaluation of efficacy. This includes trials conducted in pregnant women where there may be concerns about malformations as well as latent carcinogenic effects on the child;[38] long-term latent effect of immunisations; and the impact of drugs on latent carcinogenesis. While cohort studies are likely to provide most of the information in such situations,[38] randomised studies offer an excellent opportunity for avoiding early-acting confounders.

3. Conclusions

We have discussed some of the issues involved in the reporting of adverse effects information in randomised controlled trials. In the absence of officially developed guidelines, the recommendations summarised in table I provide some guidance the minimal requirements for ensuring that the

Table I. Recommendations for reporting safety information in randomised controlled trials

Specify the number of patients withdrawn from the study because of adverse effects, per study arm and per type of adverse effect
Use widely known, standardised scales for adverse events. If the scale is new, provide definitions for the grades of severity
Specify the schedule for collection of safety information, specific tests performed, questionnaires used and whether safety data collection and surveillance was active or passive
Provide the number of specific adverse effects per study arm and per type of adverse effect. Give exact numbers, especially for high-grade (severe and life-threatening) clinical adverse events and laboratory toxicity
Tabulation of safety information per study arm and severity grade is encouraged, as well as detailed description of cases of unusual or not previously recorded adverse effects

safety information provided by clinical trials can be readily translated to useful input for medical decision making. Other issues such as the collection and the availability of safety information from clinical trials cannot be ignored, since they are closely linked to the process of summarising and reporting adverse event data derived from clinical experiments. Randomised trials are based on the participation of human study participants who are exposed to risks that are often unknown or not quantified. The collected information is expected to be helpful both to the study participants and to many other individuals treated with similar circumstances. Quantification of the specific risks involved in the tested intervention should always be considered a primary objective regardless of the phase of the trial. In this respect, inadequate collection of toxicity data, wastage of already collected clinical information, poor reporting, and poor availability or utilisation[39] of such information are all equally ethically unacceptable. Editors of journals to whom trial reports are submitted for publication may help enforce more solid recommendations for adequate reporting of safety data by making this a prerequisite for the publication of clinical research.

References

1. Glasziou P, Irwig LM. An evidence-based approach to individualizing treatment. BMJ 1995; 311: 1356-9
2. Ziegler DK, Mosier MC, Buenaver M, et al. How much information about adverse effects of medications do patients want from physicians? Arch Intern Med 2001; 161: 706-13
3. Ioannidis JPA, Contopoulos-Ioannidis DG. Reporting of safety data from randomised trials. Lancet 1998; 352: 1752-3
4. Ioannidis JPA, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. JAMA 2001; 285: 437-43
5. Edwards JE, McQuay HJ, Moore AR, et al. Reporting of adverse effects in clinical trials should be improved: lessons from postoperative pain. J Pain Symptom Manage 1999; 18: 427-37
6. Lau J, Ioannidis JP, Schmid CH. Summing up evidence: one answer is not always enough. Lancet 1998; 351: 123-7
7. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997; 127: 820-6
8. Chalmers TC, Berrier J, Hewitt P, et al. Meta-analysis of randomized controlled trials as a method of estimating rare complications of non-steroidal anti-inflammatory drug therapy. Aliment Pharmacol Ther 1988; 2 Suppl. 1: 9-26
9. Mehta SR, Eikelboom JW, Yusuf S. Risk of intracranial haemorrhage with bolus versus infusion thrombolytic therapy: a meta-analysis. Lancet 2000; 356: 449-54
10. Schoenfeld P. Gastrointestinal safety profile of meloxicam: a meta-analysis and systematic review of randomised controlled trials. Am J Med 1999; 107: 48S-54S
11. Shah MB, Martin JE, Schroeder TJ, et al. The evaluation of the safety and tolerability of two formulations of cyclosporine: neural and sandimmune. A meta-analysis. Transplantation. 1999; 67: 1411-7
12. Stason WB, Schmid CH, Niedzwiecki D, et al. Safety of nifedipine in angina pectoris: a meta-analysis. Hypertension 1999; 33: 24-31
13. Eikelboom JW, Mehta SR, Pogue J, et al. Safety outcomes in meta-analyses of phase 2 vs phase 3 randomized trials: intracranial hemorrhage in trials of bolus thrombolytic therapy. JAMA 2001; 285: 444-50
14. Ernst E, Pittler MH. Systematic reviews neglect safety issues. Arch Intern Med 2001; 161: 125-6
15. Li wan Po A, Herxheimer A, Poolsup N, et al. How do Cochrane reviewers address adverse effects of drug therapy? In: Abstracts of the 8th International Cochrane Colloquium: 2000 Oct 25-29: Capetown. Capetown: International Cochrane Collaboration, 2000
16. National Cancer Institute. Common toxicity criteria (CTC). Version 2.0 [online]. Available from URL: http://ctep.info.nih.gov/CTC3/default.htm [Accessed 1999 Apr 30]
17. World Health Organization (WHO). Cancer treatment: WHO recommendations for grading of acute and subacute toxicity. Cancer 1981; 47: 207-14
18. Sanders C, Egger M, Donovan J, et al. Reporting on quality of life in randomized controlled trials. BMJ 1998; 317: 1191-4
19. Peloso PM, Wright JG, Bombardier C. A critical appraisal of toxicity indexes in rheumatology. J Rheumatol 1995; 22: 989-94
20. Thornley B, Adams C. Content and quality of 2000 controlled trials in schizophrenia over 50 years. BMJ 1998; 317: 1181-4
21. Stephens MD, Routledge PA, Talbot JCC, editors. Detection of new adverse drug reactions. 4th ed. London: Grove's Dictionaries Inc., 1998
22. Stephens MD. The diagnosis of adverse medical events associated with drug treatment. Adverse Drug React Acute Poisoning Rev 1987; 6: 1-35

23. Corso DM, Pucino F, DeLeo JM, et al. Development of a questionnaire for detecting potential adverse drug reactions. Ann Pharmacother 1992; 26: 890-6
24. Chuang-Stein C. Laboratory data in clinical trials: a statistician's perspective. Control Clin Trials 1998; 19: 167-77
25. Rochon PA, Binns MA, Litner JA, et al. Are randomized control trial outcomes influenced by the inclusion of a placebo group? A systematic review of nonsteroidal anti-inflammatory drug trials for arthritis treatment. J Clin Epidemiol 1999; 52: 113-22
26. Hayashi K, Walker AM. Japanese and American reports of randomized trials: differences in the reporting of adverse effects. Control Clin Trials 1996; 17: 99-110
27. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. JAMA 1996; 276: 637-9
28. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. BMC Med Res Methodol 2001; 1 (1): 2
29. Moher D, Schulz KF, Altman DG, et al. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001; 357: 1191-4
30. Shapiro SH, Weijer C, Freedman B. Reporting the study populations of clinical trials. Clear transmission or static on the line? J Clin Epidemiol 2000; 53: 973-9
31. Smith R. Electronic publishing in science. BMJ 2001; 322: 627-9
32. Hutchon DJ. Publishing raw data and real time statistical analyses on e-journals. BMJ 2001; 322: 530
33. Easterbrook P, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. Lancet 1991; 337: 867-72
34. Ioannidis JPA. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. JAMA 1998, 279: 281-6
35. Bero L, Rennie D. The Cochrane Collaboration. JAMA 1995; 274: 1935-8
36. Simes RJ. Publication bias: the case for an international registry of clinical trials. J Clin Oncol 1986; 4: 1529-41
37. McCray AT, Ide NC. Design and implementation of a national clinical trials registry. J Am Med Inform Assoc 2000; 7: 313-23
38. Irl C, Hasford J. Assessing the safety of drugs in pregnancy: the role of prospective cohort studies. Drug Saf 2000; 22: 169-77
39. Cohen JS. Dose discrepancies between the Physicians' Desk Reference and the medical literature, and their possible role in the high incidence of dose-related adverse drug events. Arch Intern Med 2001; 161: 957-64

Correspondence and offprints: Dr *Joseph Lau*, Division of Clinical Care Research, New England Medical Center, 750 Washington St, Boston MA 02111, USA.
E-mail: JLau1@Lifespan.org