



Journal watch:

Publication of clinical trial results, and guest authoring and ghost writers

by Melanie Lee

Publication of clinical trials

Clinical trial results are primarily disclosed by publication in peer-reviewed medical journals. The Food and Drug Administration (FDA) in the United States (US) mandated in the FDA Amendments Act 2007 that all trials supporting FDA-approved drugs and devices must be registered at their inception, and their basic results (demographics, number of participants who dropped out or were excluded from the analysis, and the numeric and statistical results of all primary and secondary outcomes declared at initial trial registration) should be publicly posted by the National Institutes of Health (NIH). Since 2004, members of the International Committee of Medical Journal Editors (ICMJE) have required, as a condition of consideration for publication, that all clinical trials be registered in a public trials registry before patient enrolment.

Previous research has highlighted the general problem of publication bias and incomplete or selective publication of trials in the medical literature. Lee and colleagues [1] have now analysed the literature to evaluate the publication status of trials submitted to the FDA in support of newly approved drugs, to determine how many of them are published in biomedical journals that a typical clinician, consumer, or policy maker living in the US would reasonably search. This cohort study included trials supporting new drugs approved from 1998–2000, as described in FDA medical and statistical review documents and the FDA approved drug label. PubMed and other databases were searched up to 01 August 2006, to determine publication status and time from approval to full publication in the medical literature at 2 years and 5 years. In the FDA reviews there were 90 approved drugs supported by 909 trials; only 43% (394/909) of these were published. 76% (257/340) of trials described in the FDA approved drug label, and classified as ‘pivotal trials’ by Lee and colleagues, were published. Multivariable logistic regression for all trials by 5 years post approval showed that the likelihood of publication correlated with statistically significant results (odds ratio [OR] 3.03, 95% confidence interval [CI] 1.78–5.17), larger sample sizes (OR 1.33 per 2-fold increase in sample sizes, 95% CI 1.17–1.52), and pivotal status (OR 5.31, 95% CI 3.30–8.55). Multivariable logistic regression for pivotal trials by 5 years post approval showed that the likelihood of publication correlated with statistically significant results (OR 2.96, 95% CI 1.24–7.06) and larger sample sizes (OR 1.47 per 2-fold increase in sample size, 95% CI 1.15–1.88). Publication at 2 years post approval was predicted by statistically significant results and larger sample sizes. Therefore, more than half of the trials supporting FDA approved drugs remained unpublished \geq 5 years after approval. Publication

of pivotal trials and trials with statistically significant results and larger sample sizes was more likely.

Ramsey and Scoggins have evaluated the publication of registered clinical trials in oncology [2]. They first identified oncology trials in the NIH ClinicalTrials.gov registry and then evaluated the proportion of the trials that had been published in journals listed in PubMed.gov. Of the 2,028 trials that met the inclusion criteria, 17.6% were available in PubMed. 21.0% of trials registered before 01 September 2004 were published, compared with 11.9% of trials registered after this date. 59.0% of trials sponsored by clinical trial networks, compared with 5.9% of studies sponsored by industry, were published. The results were reported as positive findings in 64.5% of published studies. Therefore, less than one in five cancer studies registered with ClinicalTrials.gov have been published in peer reviewed journals. The authors call on research sponsors, researchers, and journal editors to redouble their efforts to encourage publication of registered clinical trials in oncology [2]. Writing in *The Guardian*, Ben Goldacre comments on the findings of Ramsey and Scoggins and highlights the importance of negative data for doctors to make decisions when prescribing medication, and for academics to understand why ideas have failed when they are planning future studies [3].

Guest authorship and ghost writing

There have been further discussions about the issue of ghost writing. Liesegang and colleagues [4] have reviewed transparency in medical literature in the wake of the rofecoxib controversy, in which Merck allegedly concealed the true authorship of articles, using outside consultants or ghost writers to prepare manuscripts and then naming prestigious authorities as guest authors [5]. They considered the role and responsibility of authors, medical writers, and statisticians and how they should be acknowledged. They endorse the 11 point agenda recommended by the *Journal of the American Medical Association (JAMA)* editors, and detail their own policies to achieve more transparency and to disclose more comprehensively all the major individuals who participated in the research and manuscript preparation [4]. The actions they propose are in accordance with the ICMJE, the medical writers associations, and the pharmaceutical company guidelines.

The *JAMA* editor has received several letters in response to an editorial by DeAngelis and Fontanarosa, which discussed integrity in medical science [6, 7]. The letters cover a range of issues, including the attractions and benefits of guest authorship. The *JAMA* editor has also received a

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number of letters in response to a recent review by Ross and colleagues [5, 6], which evaluated guest authorship and ghost writing in publications related to rofecoxib in a case study of industry documents from rofecoxib litigation. Several researchers challenged claims that they were guest or ghost authors on reviews they have published, and criticised the methods used by Ross and colleagues in their analysis [6]. In reply, Ross rebuts their criticisms and provides further explanation for his conclusions.

In a recent correspondence, Adamson and colleagues discussed ethical medical writing, author accountability, and compensation [8]. They used the example of preparing a clinical trial manuscript to give a detailed analysis of the different individuals involved, their role in the process, and the appropriate way to acknowledge their contribution.

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References:

1. Lee K, Bacchetti P, Sim I. Publication of clinical trials supporting successful new drug applications: a literature analysis. *PLoS Med* 2008;5(9):e191.
2. Ramsey S, Scoggins J. Commentary: practicing on the tip of an information iceberg? Evidence of underpublication of registered clinical trials in oncology. *Oncologist* 2008;13(9):925-9.
3. Ben Goldacre. Missing in action: the trials that did not make the news. *The Guardian*, Saturday 20 September 2008. Available at <http://www.guardian.co.uk/commentisfree/2008/sep/20/medicalresearch.cancer>
4. Liesegang TJ, Albert DM, Schachat AP. How to ensure our readers' trust: the proper attribution of authors and contributors. *Am J Ophthalmol* 2008;146(3):337-40.
5. Ross JS, Hill KP, Egilman DS, Krumholz HM. Guest authorship and ghost-writing in publications related to rofecoxib: a case study of industry documents from rofecoxib litigation. *JAMA* 2008;299(15):1800-12.
6. Johnson KR, Lassere MN. Guest authorship, mortality reporting, and integrity in rofecoxib studies. *JAMA* 2008;300(8):900-4;author reply 904-6.
7. DeAngelis CD, Fontanarosa PB. Impugning the integrity of medical science: the adverse effects of industry influence. *JAMA* 2008;299(15):1833-5.
8. Adamson LM, Whitman M, Jacobs A, Bunting-Early TE. Ghostbusters should only bust ghosts. *Nat Biotechnol* 2008;26(10):1067-8.

How successful are we at understanding syntactic ambiguity?

Syntactic ambiguity is a property of sentences that may be reasonably interpreted in more than one way, or reasonably interpreted to mean more than one thing. Ambiguity may or may not involve one word having two parts of speech or homonyms.

Syntactic ambiguity arises not from the range of meanings of single words, but from the relation between the words and clauses of a sentence, and the sentence structure implied thereby. When a reader can reasonably interpret the same sentence as having more than one possible structure, the text is equivocal and meets the definition of syntactic ambiguity. Let's analyse some classic examples:

1. **Visiting friends can be boring.** *Visiting* can be boring although one can leave whenever one wants. In that sense, it is not like '*visiting friends*' who, if they stay too long, can be boring, especially if you are too polite to tell them to leave because it's your bedtime.

Now, let's disambiguate:

<i>Friends who visit [others] can be boring.</i>	<i>For one to visit friends can be boring. (i.e. visiting itself is boring)</i>
visiting friends = subject	visiting friends = subject
visiting friends = noun phrase	visiting friends = noun phrase
visiting = pre-modifier	visiting = verb (subject deleted)
friends = head noun	friends = object
can be = verb phrase	can be = verb phrase
boring = complement	boring = complement

2. **Flying planes can be dangerous.** Either *flying planes is dangerous*, or *flying planes are dangerous*.

3. **Time flies like an arrow.** Although we unambiguously understand it to mean '*Time flies in the same way that an arrow does*', it could also mean:

- measure the speed of flying insects like you would measure that of an arrow (thus interpreted as an imperative), i.e. (You should) time flies as you would (time) an arrow.;
- measure the speed of flying insects like an arrow would (this example is also in the imperative mood), i.e. (You should) time flies in the same way that an arrow would (time them).;
- measure the speed of flying insects that are like arrows, i.e. Time those flies that are like arrows;
- all of a type of flying insect, 'time-flies', collectively enjoy a single arrow (compare '*Fruit flies like a banana*');;
- each of a type of flying insect, 'time-flies', individually enjoys a different arrow (similar comparison applies);

As Groucho Marx is said to have observed, '*Time flies like an arrow; fruit flies like a banana*'.

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