

Impact of protocol amendments, bias and quality in industry-funded trials, and rethinking authorship criteria

Impact of protocol amendments

Amendments to clinical trial protocols are widespread, but can result in increased costs and delays in study implementation. Little is known about the nature and impact of protocol amendments; therefore, the Tufts Center for the Study of Drug Development (Tufts CSDD) in the USA conducted a study, in collaboration with 17 midsize to large pharmaceutical and biotechnology companies, to measure the incidence, causes, and repercussions of protocol amendments.¹ Protocols approved between January 2006 and December 2008 and across a range of therapeutic areas and developmental phases were examined, and data were collected on the protocol design characteristics; the number, nature, and causes of amendments; and the time and costs to implement these amendments. A total of 3410 protocols were submitted providing data on 3596 amendments: 54% were phase I studies, 18% phase II, 13% phase III, and 15% phase IIIb/IV.

Across all study phases, 58.8% of completed protocols had at least one amendment; 43% were amended before the first subject first visit. Each amended protocol had an average of 2.3 amendments and required an average of 6.9 changes to the protocol; later stage phase II and III protocols had a slightly higher average number of amendments (2.7 and 3.5, respectively). The therapeutic areas that had the highest number of amendments and changes were cardiovascular and gastrointestinal diseases. Larger studies and studies involving longer treatment durations were significantly positively correlated with more amendments ($P < 0.001$ using Spearman's rho correlational analysis). The most common protocol amendment adjustments made were to the population description (including inclusion and exclusion criteria; 16%) and to the safety assessments (12%). The most common causes of protocol amendments were: the availability of new safety information about the drug (19.5%), requests from regulatory agencies to amend the study (18.6%), and changes in the study strategy (18.4%); design flaws and difficulty

recruiting were also commonly cited reasons. One-third of amendments were considered 'somewhat or completely avoidable'. Each amended protocol resulted in an average of 4 months of incremental time to put into action; approximately half of this time was spent determining what changes needed to be made. The average cost per amendment was substantial (\$453 932); but this figure should be viewed cautiously as the available sample size for this calculation was small at only 20 amendments. The authors thought it important to emphasize that protocol amendments are often necessary, particularly when they impact patient safety, but suggested that their results offer insights into ways some amendments can be avoided leading to possible time and cost savings.

Quality of industry-funded versus non-industry-funded trials

In a short Current Medical Research and Opinion (CMRO) commentary, Angelo Del Parigi discussed the differences in the quality of industry-funded clinical trials compared with non-industry-funded trials.² Concerns about industry-funded trials often arise, particularly relating to fears that the commercial goals and interests of pharmaceutical companies can overrule the design, execution, analysis, and interpretation of trial results. Few researchers however have attempted to compare the quality of industry versus non-industry-funded trials objectively. The evidence so far suggests that the quality of industry-funded trials is, on average, higher than non-industry-funded trials. Del Parigi gave a few examples, such as an analysis of randomized controlled trials in a number of disease areas from a sample of Cochrane reviews that found that while conclusions tended to favour the experimental drug in industry-funded studies, they were also more likely to have larger sample sizes, more complete recording of adverse events, more frequent use of placebos or no treatment controls and double blinding, and were more likely to be published in high-impact journals compared with non-industry-funded trials.³ Other examples included a paper on long-term randomized controlled trials in obesity that found that the quality of reporting was

significantly higher for industry-funded trials and a systematic review showing that industry-funded trials had 'more complete reporting' of safety data compared with non-industry-funded trials.^{4,5}

Del Parigi pointed out that evidence of the higher quality of industry-funded studies does not excuse the presence of publication biases (e.g. selective reporting or downplaying negative outcomes) or of cases of alleged or real misconduct in industry-funded research. Del Parigi appreciated that industry-funded trials may be submitted to multiple levels of scrutiny often by external bodies, which may in part be responsible for the high-quality clinical and reporting practices associated with these trials. However, he also argued that there is still room for improvement and suggests that a first step would be to make data sets publicly available to encourage multiple independent data interpretations.

More on defining authorship

In a short *BMJ* Personal View piece, David Shaw, a lecturer in ethics at the University of Glasgow, expressed his concerns over the current and widely adhered to definition of publication authorship from the International Committee of Medical Journal Editors (ICMJE).⁶ To recap, according to the ICMJE, 'authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3'. Using

a hypothetical example of three researchers each contributing to the design, implementation, and reporting of the study in different ways, Shaw showed that none of the researchers met all three of the ICMJE criteria for authorship. Shaw took the idea further and suggested that the ICMJE criteria were unethical and should be changed because 'Having a great idea and sharing it with colleagues and approving what they do with it is clearly to cowrite a paper. Gathering and analysing data is to cowrite a paper. And redrafting and reviewing a paper is to cowrite a paper'. He suggests that the ICMJE criteria would be more sensible if they considered that meeting one of the three criteria was sufficient for legitimate authorship.

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Why won't you give me your data?

In 2005, Dutch researcher Jelte Wicherts and his colleagues contacted the corresponding authors of 141 papers published in four high-ranking psychology journals requesting their datasets to assess the impact of outliers on statistical outcomes.¹ Although all the authors had signed statements confirming that they would share their data with others to allow verification, 73% failed to do so. Why?

To answer this and other questions, Wicherts and his colleagues conducted a new study, recently

published in *PLoS One*,² in which they tested whether there is a link between willingness to share data and the strength and accuracy of statistical results. Does unwillingness to share data stem from fear that reanalysis will expose errors and challenge the authors' conclusions?

Wicherts *et al.* took a sample of 49 papers from their original study and used the information they contained – reported test statistics (t , F , and χ^2), degrees of freedom and P values – to test whether (1) accuracy of statistical reporting and (2) sizes of

P values varied according to whether or not the corresponding author had supplied the dataset.

Of the 49 reporting errors they found, a whopping 96% involved reported *P* values that were smaller than the recalculated ones. A significant majority (73%) occurred in papers whose authors had failed to provide data, while none of the corresponding authors of the seven papers in which supposedly significant *P* values were in fact found to be non-significant had given Wicherts and his colleagues their data.

In a second recent study,³ Wicherts and his colleague Marjan Bakker analysed 281 psychology papers and found that 15% of them incorrectly assigned statistical significance or non-significance to at least one result.

Further analysis in the *PLoS One* study² showed that *P* values were, on average, higher in papers whose data had not been shared. But does authors' fear of their work being undermined, of *P*

values losing their significance explain these findings?

By Wicherts and his colleagues' own admission, this is not the only possible explanation. Could it instead be the case that researchers who analyse their data with more rigour also archive them better and thus have an easier job of retrieving them on request?

Irrespective of what lies behind it, something must be done about the seemingly widespread failure to share data. According to Wicherts, what we need is for journals and other bodies to implement mandatory archiving policies. Making it impossible to publish papers without depositing the data in a web archive would surely alleviate the problem.

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How short can an abstract be?

Biomedical journals specify word limits for abstracts in the articles they publish. The upper limit is usually in the range of 100–250 words. Sometimes it is difficult to keep within these limits. However, it seems that not all authors have this problem. The abstract below appeared on the physics preprint server arXiv and was sent to *Medical Writing* by Jim Hartley (j.hartley@psy.keele.ac.uk).

Can apparent superluminal neutrino speeds be explained as a quantum weak measurement?

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Abstract

Probably not.

Keywords: Quantum measurement, interference, neutrino oscillations

Source: <http://arxiv.org/abs/1110.2832>

Conflicts of interest: what do peer reviewers think?

Whether or not industry sponsorship causes bias in scientific papers has been much debated. On the other hand, until now, no one has looked at whether conflicts of interest influence how peer reviewers view and review manuscripts.

To explore peer reviewers' feelings about financial conflicts of interest, Suzanne Lippert and her colleagues sent a 29-question web-based survey to 410 active reviewers for *Annals of Emergency Medicine*, one of the many journals that now

require authors to make statements regarding their conflicts of interest.

Most of the 218 reviewers who provided complete responses to the survey felt that authors were influenced by their financial ties to industry.¹ However, this did not clearly translate into changes in the way they evaluate manuscripts.

While a majority of reviewers claimed that they would read more carefully papers whose authors had conflicts of interest, and felt that the credibility of such papers would be reduced, considerably fewer would change their recommendations to the editor.

In their responses to one particular question, three-quarters of reviewers expressed doubt as to whether authors of industry-sponsored articles have full access to data. Meanwhile, a small majority (54%) believed that an honorarium of any size biases an author's judgement, which does not exactly lend support to Lippert *et al.*'s proposal that authors divulge the *sizes* of the payments they have received from companies.

Interestingly, a smaller proportion of reviewers who themselves had received such payments considered that they cause bias. Do the experiences of these reviewers not square with the suspicions of those who have never consulted for pharmaceutical companies? Are academics who do not believe that honoraria cause bias more likely to accept them? We can but speculate.

Lippert *et al.* further suggest that authors confirm that they had full access to the study data, while acknowledging that this is already covered by ICMJE guidelines.² Their third key proposal—that peer reviewers themselves disclose industry payments—is, and has long been, a stipulation of the journal whose reviewers they surveyed.^{3,4}

In other conflict-of-interest news, David Isaacs, Editor-in-Chief of the *Journal of Paediatrics and Child Health*, has written an editorial warning of the dangers of financial conflicts of interest and refuting the notion that declaring them does anything to prevent bias.⁵

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