Proposed best practice for statisticians in the reporting and publication of pharmaceutical industry-sponsored clinical trials

James Matcham, a Steven Julious, b Stephen Pyke, c Michael O’Kelly, d Susan Todd, e Jorgen Seldrup, f and Simon Day g

In this paper we set out what we consider to be a set of best practices for statisticians in the reporting of pharmaceutical industry-sponsored clinical trials. We make eight recommendations covering: author responsibilities and recognition; publication timing; conflicts of interest; freedom to act; full author access to data; trial registration and independent review. These recommendations are made in the context of the prominent role played by statisticians in the design, conduct, analysis and reporting of pharmaceutical sponsored trials and the perception of the reporting of these trials in the wider community. Copyright © 2010 John Wiley & Sons, Ltd.

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1. INTRODUCTION

The proposals by the editors of the Journal of the American Medical Association [JAMA] [1] for the reporting of industry-sponsored clinical trials have resulted in widespread discussion among editors of medical and statistical journals as well as amongst statisticians who work within the pharmaceutical industry [2]. The signal from JAMA seems to confirm a fear we perceive is held by many academic researchers that clinical research sponsored by industry is potentially biased with the design and reporting of trials suspect due to the inherent financial conflict of interest of pharmaceutical industry staff. This may also be influencing the wider medical community to share these concerns.

This suspicion seems to be restricted to industry-sponsored trials as scientists working on clinical trials in academic public health centres are perceived to be independent of financial conflict. One explanation for this could be that the success of their sponsor (usually a grant funding body) is not dependent on the successful outcome of the trials they sponsor. The same does not hold for industry-sponsored research. The academic independence of the results of trials and the success of their sponsor is the key reason underpinning the academic freedom and independence claimed by academic researchers.

Of course there are other conflicts of interest that all researchers are open to, irrespective of their source of funding. These include conflicts that are born out of some form of personal gain, which could be garnered from an enhanced academic reputation which could facilitate professional advancement. Academic pressure to publish in high impact publications could lead to selective reporting of results and over statement of results, which themselves could be sources of bias.

The main tool used by journals to maintain scientific standards is peer review with conflicts of interest addressed by a need for disclosure by each author of the paper. The expectation seems to be that this approach both ensures appropriate standards are maintained while identifying papers with potential for bias.

The reporting of clinical trials in journals has rightly received attention from journal editors in the past. For example, the CONSORT group was formed and published recommendations for reporting trials [3], which have been revised [4] and extended to the reporting of non-inferiority/equivalence studies [5] as well as other forms of empirical clinical research [6]. In addition, concerns over ghost authorship [7], restrictive clauses in clinical trial agreements [8] and inappropriate delays in publishing trials [9] have also been voiced. The aim of this paper therefore is not to deal with the appropriate content of a clinical trial report, but to focus on the best practices for the reporting of clinical trials and in particular to make some proposals for best practice for statisticians involved in the reporting of industry-sponsored clinical trials.
Elsewhere in this issue, an overview of the potential for bias in the reporting of industry-sponsored trials is discussed by Pyke et al. [10] while public disclosure of industry-sponsored trials is surveyed by O’Kelly [11]. The proposals we put forward here represent the views of the authors but it is our hope that the publication of these proposals will ignite a more general debate amongst trial statisticians from pharmaceutical companies and other sponsoring groups. By proposing these guidelines we particularly highlight the important role played by the trial statistician as an author of the published clinical trial report.

2. BEST PRACTICE FOR STATISTICIANS IN THE REPORTING AND PUBLICATION OF INDUSTRY-SPONSORED CLINICAL TRIALS

Any best practice recommendations should promote the role of all authors in taking the responsibility for the planning, design, conduct, analysis and reporting of the results of the trial. In many instances, the trial statistician will be the person with the most in-depth knowledge of the data and so should take particular responsibility for the full and accurate reporting of the results and the statistical interpretation. This should include a responsibility for making sure that all the authors have had full access to the data, to the analyses that have taken place and to the statistical interpretation of the results so that the authors are able to form appropriate clinical and medical interpretations of the trial results.

It is in this context that we make the following recommendations.

1. The statistical author should be responsible for the statistical aspects of the paper

The authoring statistician should take responsibility for the statistical content of the paper. This should include, but is not restricted to, the correct statement of the trial objective and endpoints, the sample size justification, patient flow, analysis data set definition (e.g. Intent to Treat, per Protocol), presentation of the results and statistical interpretation of the results. It is also important that the paper appropriately identifies the methods that were planned in the original protocol and justifies any deviations from this in the final analysis results that appear in the paper.

2. The person responsible for statistical aspects of the trial should be recognised as an author

Subject to the framework for authorship established by the International Committee of Medical Journal Editors (ICMJE) [12] the statistician who is responsible for the design, conduct, analysis and reporting of a clinical trial should be identified and named as an author of the publication. They should be appropriately qualified and experienced. Where papers are submitted with no statistician declared as an author, this should be noted and justified. If the trial has included a Data Monitoring Committee (DMC), the trial statistician should ensure that any statistician member of the DMC and any statisticians supporting the work of the DMC are identified and their role in the trial should be summarised. This should include the specific duties of the DMC statistician and the recommendations that they contributed to.

3. Protocols should be published and/or made publicly available in a timely manner

There should be a clear means for journal reviewers and editors to confirm the pre-defined study objectives, endpoints and methods of analysis through having access to a publicly available protocol. This would enable them to confirm whether the published record of the trial adds, changes or omits important elements of the trial as conceived and set out in the protocol. It would also make clear where any results have been held back or retrospectively added. Publishing these details on a publicly accessible trial registry goes some way to addressing this and it is recommended that should be routine practice to include the pre-defined statistical methods of analysis for key trial outcome measures. The trial statistician should ensure that the protocol materials published include all the relevant details so that a subsequent reviewer can readily identify the trial objective, endpoints, design, sample size and proposed method of analysis for the primary endpoint.

4. Financial and other conflicts of interest should be disclosed

There should be a clear statement identifying who sponsored the trial. The trial statistician could be a sponsor company employee and/or employee of a contract research organisation who has been contracted by the sponsor to take the role of the trial statistician. They could also be an employee of an academic organisation who is running the trial with an industrial sponsor. Along with the other co-authors, the trial statistician should declare any financial interest and conflict of interest in terms of their employment status together with any direct and indirect financial interests in the sponsor and/or other relevant companies.

5. The authors should have freedom to act

The primary investigator and other co-authors should not be pressured by any sponsor company, either contractually or otherwise, to suppress the publication of trial results, or present the trial in a manner that they feel to be inappropriate. Freedom to act is particularly relevant to the trial statistician. There should be no impediment to the trial statistician in their role as author to appropriately presenting trial results. The trial statistician should understand that by being an author they are taking professional responsibility for the accurate reporting of the trial and that the results as presented are a true and fair reflection of the outcome of the trial.

6. All authors should have full access to trial data

The authors of the trial manuscript should have appropriate access to the data collected during the trial and should have played full part in the interpretation of the results from the trial. In particular, they should have access to the data set used for the analysis and they should have access to the results of all the analyses that have been conducted. An important duty for the trial statistician is to ensure that the data and results of the trial are presented to each of the authors in a timely manner.
They should also ensure that the authors can access and understand the results and should facilitate communication between all authors to satisfactorily address any questions.

7. The trial results should be published

All trials should have their results published in publicly accessible registries designed for the purpose. This should also be done in a timely fashion after the completion of the trial (no more than one year after last subject last visit is good practice). As appropriate it is recommended that the trials are also published in peer review journals. Any publication should be identified and linked to the previously published trial protocol. The trial statistician should ensure that the results are made publicly available in a manner that is understandable to the wider medical community and is complete such that all results are disclosed and others are able to use the results in further research (e.g. meta analyses).

8. Independent statistical review should be highlighted

Many industry-sponsored clinical trials undergo some form of statistical review by independent experts and/or regulators (e.g. available from published FDA Advisory Panel materials and European Public Assessment Reports) both in the design and in the review of the results. Where this takes place, the nature and scope of independent review should be described in the published manuscript. Where the review has been paid for, a statement should be made clarifying the nature of the relationship between sponsor and expert.

3. DISCUSSION

Our recommendations are, we believe, practical to implement in companies of any size and we hope represent best practice. The important thing to highlight is that all authors have responsibilities with respect to the results of the trial and the statistician has particular and specific responsibilities.

We hope these recommendations will help start a discussion among interested parties and welcome suggestions to improve and strengthen them. Some issues we have already identified as worthy of further consideration include the following points.

- Electronic access to the CVs of each author so that readers could identify that authors are appropriately trained and qualified to take on the role identified in the paper.
- The discussion and proposal of best practices for statisticians working on non-industry and industry-sponsored studies should jointly be published by a suitably qualified group.
- All clinical trials submitted for publication should undergo statistical review by appropriately qualified and suitably experienced statisticians.

We believe that it should now be possible to achieve a consensus in each of these areas. More controversially, it has been suggested that;

- Anonymized individual patient data, compliant with laws on personal protection and privacy, could be made publicly available. There are possible negatives to this: for example it could lead to hostile trawling for unfavourable results using unplanned analyses [13]; for trials of non-approved drugs there are also competitive considerations. However, we believe such an approach would complement the emerging interest in pre-competitive knowledge sharing that is seen in the early pre-clinical arena.
- Regulatory bodies publishing more detailed reviews of trials in a publicly accessible way. This in turn would link into the timely publication of results.

We believe both these interesting proposals merit further discussion.

4. CONCLUSIONS

The proposals we set out in this paper are intended to encourage debate and also to form a basis for good publication practice for statistical authors, particularly those in the pharmaceutical industry.

The role of the trial statistician is to play a full and pro-active part in the design, conduct, analysis, reporting and interpretation of the trial and to be accountable for reporting the statistical aspects of the trial.

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REFERENCES


