

Publishing clinical trials: Ethics and the pharmaceutical industry¹

A Joint Symposium by the European Medical Writers Association and the Institute of Clinical Research

by Nancy Milligan and Andrew Smith

February 27th 2008 saw the first joint symposium held by the European Medical Writers Association (EMWA) and the Institute of Clinical Research (ICR). Nearly 100 members of the two professional organisations gathered in London to discuss the ethics and best practice of publishing clinical trials.

Publications: Purpose & process

Julia Donnelly, Julia Donnelly Solutions Ltd

Julia gave an overview of publications in clinical research, from conference posters to peer-reviewed journals. She began with some examples of bad publication practice: over-reporting of positive results (whether deliberately or inadvertently, as a result of over-enthusiasm), under-reporting (or not reporting at all), and ghostwriting.

She went on to consider posting of protocols and summary results on registry websites. Trial results are often published within weeks or months of the last patient's last visit, although such tight timelines can cause problems for medical writers. This early publication can encourage a peer-reviewed journal to also publish the study rapidly, but lacks any interpretation or expert opinion, and may negatively affect the decision of a peer-reviewed journal to publish.

Julia discussed the criteria for authorship: conception or development of the study, acquisition or analysis of data, and involvement in preparing and approving the paper. Ideally, an author should meet all criteria.

In conclusion, Julia stated that publications are highly regarded overall, and that it is possible to develop ethical publications, but it is important to follow the guidelines.

Fraud in publications

Harvey Marcovitch, Chairman, Committee on Publication Ethics (COPE)

Harvey Marcovitch began by discussing several cases of fraud, including that of Jon Sudbo, who published 38 peer-reviewed papers and was awarded a \$10m grant before admitting fraud in 2006.

He referred to principles of publication ethics and the Declaration of Helsinki, which are referred to in the International Committee of Journal Editors (ICMJE) guidelines, and summarised the cases discussed by COPE; falsification was mid-way through the list (behind duplicate publication). Competing interests are common: a quarter of researchers have received pharmaceutical funding, while 1 in 3 had a financial interest in their work. In 2001, only 54% declared this interest. There appears to be a correlation between positive 'spin' on results with competing interest.

He went on to discuss 'missing' negative studies and the impact this can have on meta-analyses, and the ways in which fraud is detected. Even when detected, fraud is sometimes not reported for fear of recriminations from the fraudulent author. Signs to watch out for are studies that are unfeasibly large for the authors' resources, the data looking 'too good to be true' or counter-intuitive, or if the author puts undue pressure on the editor. Editors should be prepared to act on complaints about old publications, remembering that dishonest people are often dishonest more than once. Publishing declarations of concern, corrections and retractions are important measures for the future as well as for the scientific record.

There are many obstructions to investigating fraud: they are difficult and costly, and institutions can be in denial, whether due to their own conflicts of interest as employers, poor experience of conducting investigations and the increasingly international nature of research.

Authorship, guests & ghosts

Elise Langdon-Neuner, Director of Preclinical Documents & Scientific Communications, Baxter BioScience, Austria

Elise Langdon-Neuner spoke on guest- and ghost-authorship: a guest author is an author but shouldn't be, while a ghost author isn't an author but should be. Most guest authors are departmental heads, perhaps on the basis that having a 'big name' author can boost acceptance chances.

Elise next discussed why writing assistance is not acknowledged as authorship: ignorance, embarrassment and deceit. She called for all those involved in writing and approving content (including medical writers and publication managers) to be acknowledged. In looking for ghost authors, ICMJE guidelines state that editors should specifically ask for additional contributors not named by the authors.

Elise pointed out that very few journals have adopted the concept of contributorship, embodied in the ICMJE guidelines, to replace authorship. Of those that do ask for contributor statements, there is little if any vetting, and a study showed 70% unreliability between forms completed twice by the same authors.

Looking at why the ICMJE guidelines fail, Elise reported that many authors are not aware of, ignore or disagree with them. However, not even all journals use the guidelines: in one study only 29% of 234 journals' guidelines are based on them. Even one member of the ICMJE committee admits that the guidelines have serious flaws.

¹ This report of the joint conference will also be published in the ICR members' journal, *Clinical Research focus*

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Elise also discussed guidelines by the World Association of Medical Editors (WAME), which suggest that editors should alert the author's institution and share the information on the WAME list-server. However, again, not everyone is doing this; there is little incentive for publishers, pharmaceutical companies and the scientific community. The only people who are suffering are junior staff who are excluded from authorship, and the public who are receiving distorted information.

Ghostwriting: What's the problem?

David Healy, Professor of Psychiatry, Cardiff University

David Healy spoke on the drivers behind ghostwriting, including the potential for a pharmaceutical "blockbuster" to make or break a company and the increasing involvement of specialist medical writers alongside (or instead of) the independent investigators. He analysed the work of one medical writing firm, contrasting the impact factors and citation rates of their papers with other papers with the same named authors, and concluding that their involvement had had a significant influence.

He then considered the notion of 'disease mongering', and the influence of early papers in defining guidelines for future treatment, cementing the place of those treatments in the market. He suggested that this underpins companies' selection of authors and target journals.

David looked at studies on paroxetine (a selective serotonin reuptake inhibitor (SSRI), one of his areas of interest), in which many serious adverse events were not reported, and showed correspondence relating to the articles, demonstrating the conflicts of interest and their impact. He further discussed a meta-analysis of suicidal acts with SSRIs which was declined for publication and listed a number of journals where his own articles were declined for 'legal reasons' and fear of litigation.

He finished by stating that the altruism with which people have taken part in clinical trials since the 1950s has been undermined by the activities of pharmaceutical companies in restricting the publication of their results.

Panel discussion

Closing the morning session, the speakers took part in a panel discussion. The first two questioners asked why protocols are not routinely sent with article submissions and why submitted papers are not routinely checked against their registry entries. In both cases Harvey Marcovitch said that this was simply a matter of insufficient resources, but reviewers are now able to check.

The next questioner discussed ghostwriting, highlighting the difference between preparing the paper with clarity and following guidelines, and taking responsibility for the scientific decisions, analysis and interpretation in the paper. David Healy responded by saying that this wasn't so much the problem but that the raw data should be made publicly available for verification. Delegates responded by suggesting that this should be extended to all studies, not just those sponsored by the pharmaceutical industry.

A delegate questioned the role of the regulatory authorities in determining whether the full data from a study had been made public. There was some disagreement on whether regulators analyse study data or just examine expert reports, and whether requested data is given, in full or in part. Another delegate suggested that protocol and result registries would aid this although David argued that the raw data should be published rather than summary reports. Harvey welcomed this development, but also expressed anxiety about the completeness of the data, particularly the reluctance of pharma companies to share commercially sensitive information during a competitive time window.

A journal editor's perspective of industry practices

Trish Groves, Deputy Editor, British Medical Journal (BMJ)

Trish Groves, deputy editor of the *BMJ*, gave her viewpoint as a journal editor. Trish discussed article placement in journals, suggesting that primary research articles *create* influence while secondary articles *spread* influence. She talked about the journal acting as a gatekeeper, having its own brand and commercial interests, and outlined the *BMJ* brand of aiming to help doctors make better decisions; providing truthful, clear, and engaging writing; and taking a tough stance on misconduct. She suggested that research misconduct is widespread, but it is hard to detect and stop. She also argued against the belief that journals are anti-pharma.

Trish went on to discuss transparency in reporting, mentioning a 2006 *BMJ* paper which suggested that industry-sponsored reviews were of lesser quality than Cochrane reviews, and how results were always in favour of the sponsored drug. However, a similar study in 2007 suggested that things had improved, but there was still a problem with the conclusions drawn from data. She suggested that there is some 'spin' in all research articles and that there is an argument that articles should end after the results section to leave readers to draw their own conclusions from the findings. The counterargument is that this would make articles difficult to read by not placing the results in context.

Her four simple points of advice for dealing with journals effectively were: get to know the journal and their brand, follow the editorial instructions and policies, ask the editor's advice before submission, and don't be afraid to tell the truth; her phrase was "Life is messy; show us your mess". She also outlined the *BMJ's* requirements for papers on drug trials: transparency policy, request of the protocol, statements, registration, and compliance with guidelines.

The new Food and Drug Administration requirements on registration and disclosure of trial results were then talked about. For example, it is now a requirement to register the trial (on clinicaltrials.gov) and provide tables (both raw data and statistical tests) for outcome measures and information on adverse events grouped by organ system. In addition, results must be posted within a year.

Trish concluded by discussing transparency in secondary (review and educational) research articles. At the *BMJ* they ask: have you been asked to write this (referring to

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commissioning), have you been paid to write this, did a professional writer work on this? She assured that even if the answer to any of these questions is yes, the article will still be considered for publication. It seems that it is the transparency that is the key.

Publication policies: Why every company needs one

Liz Wager, Publications Consultant, Sideview

Liz Wager's presentation focused on publication policies stating that every company should have one and keep it up to date. Liz started by looking back to the 'dark ages' when drug companies used to have a free rein with study data and frequently used ghostwriters, but this meant that the scientific record was distorted and consequently patients suffered. Now things have changed, journal editors ask more difficult questions and companies can be sued for non-publication of results. She also made the point that editors can now publish damning reports if companies misbehave.

Liz went on to distinguish between professional medical writers and ghostwriters and talked about the EMWA guidelines, which state that the use of professional writers should be acknowledged.

She then examined the risks of not having a publication policy, these were: authorship disputes, delayed publications or rejections, poorly informed and inconsistent publication decisions, and negative publicity. Conversely, the benefits of having one include: it is an efficient way of working which survives despite staff changes, it facilitates internal and external communication, and it strengthens relationships with authors and editors. The importance of devising this policy early enough and integrating it with the protocol and study negotiations was also highlighted. She suggested the process of developing a policy is also useful, and that it should become part of a company's brand and identity (i.e. being ethical can be a selling point).

Liz went on to discuss various elements that should be included in a publication policy. For drug companies, she suggested: investigator contracts, access to data, authorship policy, commitment to publish all trials, and the right to comment and/or delay trial registration. For agencies, she suggested: policy for acknowledgements, process (e.g. good publication practice [GPP]) and quality (e.g. CONSolidated Standards Of Reporting Trials [CONSORT]) standards, avoiding redundant publication and plagiarism. She closed her presentation by running through the guidelines available, including the Declaration of Helsinki (which is committed to publishing negative findings), ICMJE, EMWA, and GPP.

The view from 'big pharma'

Valerie Siddall, Global Director of Publications, AstraZeneca

Valerie Siddall closed the day by giving the perspective of a pharmaceutical company. Valerie started by suggesting that publication policy is about reputation, so everyone in this industry should really care about it. She argued that single events are behind headlines, and that single events

can affect reputations that may have been built up over many years. She went on to suggest that publication policies should be clear, current, well-communicated, widely understood, and followed.

Throughout her presentation, Valerie gave her 'top tips'. One of these was "if you have a publication policy, share it" with internal staff and external providers (for example, investigators, contract research organisations, collaboration groups, authors, communications agencies/writers, licensing partners). Valerie talked about giving careful thought to communication and training in the publication policy, she suggested important factors were: sponsorship at the most senior level, having a passionate owner, targeting to your audience, and making it relevant, interesting, and fun.

She then discussed factors important in the effectiveness of a policy (coverage, clarity, consistency, level, differentiation versus other pharma companies) and how staff and agencies must follow the policy (compliance, use of internal audit group).

She concluded her presentation by suggesting that policies are tested by getting the opinions of investigators and authors, and reiterated the importance of keeping the policy current by using regular review cycles.

Panel discussion with Q&A

Some interesting points were raised in the panel discussion at the end of the afternoon, based primarily on the topic of publishing research results. One delegate thought that it was worrying and impractical for pharmaceutical companies to have to publish all results, and that there would be an information overload if all data were available in this way. They went on to suggest that it would then be difficult to distinguish what was relevant and what wasn't. Members of the panel suggested that it is most important to publish trials related to marketed products; in other words that it is ethical for companies to publish all data for a product that is being sold. During the discussion, it was also suggested that systematic reviews could be used to prevent information overload and remove bias from results. It was also pointed out that programmes such as CDISC could be used to make raw data available. The final discussions centred on whether there is an ethical obligation to publish and whether medical writers have a responsibility to be ethical.

Conclusion

In conclusion, this proved to be a very interesting, lively, and sometimes controversial day symposium, which was enhanced by the interesting variety of speakers who all had their own differing viewpoints on the current role of ethics in publishing clinical trials. Here's hoping that similar, equally successful symposia will be organised jointly by the ICR and EMWA in the future.

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