



Transparency in disclosure of clinical trial information

By Ruth O'Halloran

Unfortunately we live in a society where loss of trust is a recurring theme: loss of trust in government, religion, the law... In terms of conduct of clinical research, loss of trust is not surprising considering recent scandals associated with the pharmaceutical industry, which have also resulted in a loss of trust in government agencies such as the Food and Drug Administration (FDA). During 2005 tremendous change was instigated to affect a significant improvement in transparency and accountability of how clinical research is conducted and reported.

Background

Evidence-based healthcare is dependent upon published research—where else would decision or policy makers get their information? However, we constantly read that medical literature is distorted by publication bias. Publication bias arises from differential reporting of study results depending on the direction and strength of the findings; therefore, entire studies may fail to reach publication, or specific results within a study may not be reported (selective reporting) because of the nature of the findings. Often there are reasons why results from clinical research may fail to reach publication, some of which include: null results; not an important result; unfavourable results; sponsor has control of data; analysis incomplete; study incomplete; rejection from journals. This results in publication bias, which has negative effects on science (redundant publication of positive findings; wasteful duplication of research) and medical practice (review articles may be misleading when they are only based on some of the evidence). Moreover, entities conducting clinical research have an ethical responsibility to trial participants to report the findings from their research.

Change: why now?

In recent years numerous guidelines have been developed in an attempt to improve the quality of publications and promote good publication practice [1-3]. In September 2004, the International Committee of Medical Journal Editors (ICMJE), which comprises the world's most influential journals (see Table 1), stated that, as a condition of consideration for publication, they will require proof that all clinically directive trials (primarily phase 3, excludes phase 1) were registered in a public trials registry prior to when the first subject was enrolled [4]. What can perhaps be counted as the most significant event on the road to eliminating publication bias occurred when this became a

mandatory requirement for manuscripts submitted to ICMJE member journals for clinical trials starting on or after 1 July 2005. All clinical trials ongoing on this date were required to be registered on or before 13 September 2005. While this requirement is only for ICMJE member journals, there is little doubt that other journals will follow suit.

Clinical trial registries

The rationale for registries was to increase subject recruitment (inform patients and clinicians about recruiting trials), to complete the evidence base by eliminating publication bias, and to reduce duplication of effort in research.

In the influential September 2004 statement, the ICMJE endorsed the US National Library of Medicine sponsored registry: www.clinicaltrials.gov. In their July 2005 follow up statement [5], the ICMJE insisted that registration of a clinical trial should comply with the World Health Organisation (WHO) minimal data set, which contains 20 fields [see www.who.int/ictrp/en for details].

Currently there are only two registries accepted by the ICMJE: www.clinicaltrials.gov and www.isrctn.com (the

Table 1: International Committee of Medical Journal Editors (ICMJE) Member Journals

ICMJE Member Journals
Annals of Internal Medicine
British Medical Journal
Canadian Medical Association Journal
Croatian Medical Journal
Journal of the American Medical Association
Nederlands Tijdschrift voor Geneeskunde (The Dutch Medical Journal)
New England Journal of Medicine
New Zealand Medical Journal
The Lancet
The Medical Journal of Australia
Tidsskrift for Den Norske Llegeforening
Ugeskrift for Laeger (Journal of the Danish Medical Association)

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International Standardised Randomised Clinical Trial Numbering scheme). However, it seems that every region, country, state and company have developed or started to develop their own registry. To date the number of active registries is enormous, some of these include: Australian Clinical Trial Registry (ACTR) [www.actr.org.au]; Canadian registry (www.canadatrials.com); European clinical trials database (EudraCT) [www.eudract.emea.eu.int: to be incorporated into the proposed EUROPHARM database]; Japan Pharmaceutical Information Center (JAPIC) [www.japic.or.jp]; South African National Research Register (SANRR) [www.sanrr.gov.za]; UK National Research Register (NRR) [www.nrr.nhs.uk]. In February 2005 new legislation (Fair Access to Clinical Trials Act) was introduced to US congress stipulating mandatory registration of clinical trials and mandatory reporting of clinical trial results. Now there are 22 states in the US with proposed legislation for registries. In addition, there are >300 commercial and disease specific registries available, not to mention a large number of company specific registries.

This explosion of growth in the number of registries raises problems such as: How many registries is enough? Which registry to choose? What about certification of registries? How will unique trial identification numbers be assured? How will compliance be monitored? What about the quality of the data entered?

Thankfully the WHO has taken a leadership role and developed an International Clinical Trials Registry Platform (ICTRP) [www.who.int/ictrp/en], through which all WHO certified registries will be accessible. It is planned that this will be an internationally accepted centralised repository for clinical trial information (registries and results), and fully functional by 2008. Clinical trials will be unambiguously identified using uniform standards. The WHO will also provide certification of acceptable registries and promote compliance.

As the ICMJE imposed deadlines passed, interested parties kept a watchful eye on compliance in registering trials and also on the quality of the data entered. A review of trial registration at www.clinicaltrials.gov during the interval May to October 2005 showed that there was a 73 per cent increase in the number of trials registered during this time (note: this time interval incorporated the final ICMJE deadline of September 2005) [6]. The authors concluded that, although data records were more complete than trials registered previously, there is still room for improvement.

Pharmaceutical industry response

The pharmaceutical industry (see Table 2 for member associations) released a joint position statement in January 2005 recognising the public health benefit of registries [7]. In addition, the pharmaceutical industry committed to posting clinical trial results to a free, publicly accessible results database, regardless of the outcome. Results will be posted within one year after a drug is first approved and commer-

cially available, or one year after trial completion. Summary information will be presented in an objective, scientific format (non-promotional and in accordance with the International Conference on Harmonisation [ICH] E3 guideline [8]) and fully report study findings including all primary and secondary outcomes, and safety. These summaries are not intended to replace patient-physician interaction, the comprehensive nature of the product label or be a substitute to a peer-reviewed publication, nor should they be a barrier to peer-reviewed publication. A number of companies are using the Pharmaceutical Research and Manufacturers of America (PhRMA) sponsored website www.clinicalstudyresults.gov, while others are using their own company websites. Recently, the Federation of Pharmaceutical Manufacturers and Associations (IFPMA) established a portal enabling access to all industry sponsored websites [www.ifpma.org/clinicaltrials.html].

Currently there is no mandate for disclosure of clinical trial results; it is voluntary. However, the WHO has indicated that they will establish results disclosure standards. As we move forward, there will need to be a traceable link between registration and results reporting, as well as consistency—meaning that either trialists or the WHO will need to exercise due diligence to ensure registries and results databases are kept up to date.

Conclusion

Future success of the above initiatives will be dependent upon, and primarily driven by, the WHO taking a leadership role in providing globally harmonised standards and processes. Many challenges lie ahead for management, compliance and consolidation of the numerous registries and results databases that have emerged. Issues still needing consensus include: creating a genuine balance between transparency and intellectual property; addressing the number of registries, including their credibility and quality; defining roles and responsibilities; establishing globally harmonised standards and processes.

There is no arguing that the combined effort from all trialists over the last year has resulted in a positive step forward toward improving transparency in disclosure of clinical trial information, albeit with lots of room for further improvement...

Table 2: Pharmaceutical Industry Associations

Pharmaceutical Industry Associations
Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
European Federation of Pharmaceutical Industries and Associations (EFPIA)
Japanese Pharmaceutical Manufacturers Association (JPMA)
Pharmaceutical Research and Manufacturers of America (PhRMA).



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Affiliations/Competing interests

Ruth O'Halloran is an employee of Pfizer Worldwide Development Operations, Sydney, Australia. Ruth is involved with registration and results database activities for Pfizer clinical trials in the Asia region and has presented regularly on this topic. This article has been submitted by Ruth on behalf of the Australasian Medical Writers Association.

Ruth O'Halloran

Asia Biometrics Centre, Pfizer Worldwide Development Operations, Sydney, Australia
ruth.ohalloran@pfizer.com
www.pfizer.com.au

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Authorship, accountability and communication professionals

As the world recovered from the South Korean stem cell fraud [1], the American senior author of one of the articles retracted from the journal *Science* was being investigated to elucidate his possible role "in the fabrication and falsification of the data" [2]. The investigation disclosed authorship practices that EMWA members may find unusual.

Dr Schatten was not involved in data acquisition, analysis or oversight despite his role as senior and corresponding author, but his disengagement is hard to infer from the authorship and funding information in footnote 32 (reproduced in the University of Pittsburgh panel's report) of the *Science* article. He did not fulfil the criteria for authorship [3,4], and although he accepted "the responsibility that all authors [...] have seen and approved the manuscript, its content, and its submission to *Science*" [5] it was later discovered that many authors had not read the paper until after it was published. However, he participated enthusiastically in the "reputational enhancement" that followed publication, and may have been instrumental in getting the paper accepted for publication [6,7]. Later he abruptly dissociated himself from the study when ethical problems came to light.

Would a communication professional have claimed authorship and then tried to evade responsibility when serious ethical problems were identified? Not if he or she espoused the Good Publication Practice recommendations [8] and EMWA's professional code of practice [9]. The latter notes that "by agreeing to be listed as an author, the medical writer takes public responsibility for the research." Public claims of authorship credit bring public

accountability for the content, both for researchers and for the communication professionals who aid them. Schatten, a researcher, was apparently paid large sums of money by lead author Hwang and was also rewarded with senior authorship. Yet had he been a medical writer instead of a researcher, his behaviour would be considered unprofessional and unethical, not merely "misbehavior" [2,6].

The incident shows that the roles of authors and communication professionals need to be carefully distinguished, and that all contributors regardless of their role need to be held publicly accountable for their input.

Karen Shashok

Translator and Editorial consultant, Granada, Spain.
E-mail kshashok@auna.com

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