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Editorial

Can we do better at registering clinical trials?

In today's medicine, the importance of making clinical decisions based on evidence from prospective randomized control trials is now thoroughly accepted. However, decisions are rarely taken based on the results of a single study, since it is also accepted that few interventions are without unwanted as well as wanted effects. Practitioners and professional bodies consider the evidence from all studies and modify their practice and recommendations after weighing the pros and cons of any intervention. A correct decision can only be taken if it is based on complete evidence.

There are dangers, of course, if the scope of evidence under consideration is incomplete. Unfortunate instances where only part of the picture was presented have led to prescriptions and practices that unnecessarily endangered the lives and health of patients. Publication bias, where only positive results have been published, are not uncommon; in some cases leading to unfounded claims for a particular therapy [1] and in others resulting in life threatening side-effects omitted from the literature [2]. In the digital world of today, a biased article once on the Internet has a potentially infinite audience.

It has been apparent to most professionals for some time that transparency is necessary to (i) guarantee unbiased reporting of results of all clinical trials to avoid publication bias, (ii) prevent unnecessary duplication or repetition of studies previously or simultaneously being conducted, (iii) improve internal as well as external validity of results, and (iv) fulfill the ethical responsibility of researchers to protect the public's access to results that could impact on health.

In 2004, the International Committee of Medical Journal Editors (ICMJR) published a statement in the New England Journal of Medicine calling for prospective registration of all clinical trials. As a start, they announced that evidence of registration would be compulsory for publication in any of the journals of the Committee [3]. They advocated for all other editors of biomedical journals to adopt the same practice. Obligation to register in order to be considered for publication was detailed in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URM) in 2007 and reiterated in the revised requirements in April 2010 [4]. In the United States, mandatory registration and results reporting were written into public law in 2007 (see http://clinicaltrials.gov/ct2/invest) in recognition of the key importance of registration of trials along with the complete and conscientious reporting of results. The World Medical Association included the requirement for preregistration of clinical trials in the Declaration of Helsinki in its various iterations, including the latest in 2008 [5].

Unfortunately, compliance globally has been inadequate. In this issue of *Asian Biomedicine,* Tulvatana *et al.*, report three alarming statistics about compliance with compulsory registration of clinical trials. In a survey of 87 of the highest impact journals in ten leading specialties of medicine, they report that less than 60% of these journals have signed on with instructions to authors requiring a pre-registration number. Of those that have required evidence of registration for publication, only 35% followed the requirements strictly. Furthermore, of the 57 journals whose editors are members of the Committee on Publication Ethics, only 31.6% reportedly complied with the regulation, a number not significantly different from those whose editors were not members. Tulvatana, *et al*. are not alone in reporting this discouraging information. Similar results have been described in Mathieu, *et al.,* of adequate registration of only 45.5% of trials screened [6], and by Shamliyan and Kane, who found that results were unavailable in more than half of the studies they surveyed involving children [7].

These numbers are disturbing for what they say and for what they imply. The first concern should be for those journals described by Tulvatana, *et al.,* that have 'signed on' to compulsory registration but failed to enforce it. We can only conjecture at what is behind this: impatience with bureaucratic steps necessary for registration; reluctance to miss out on a 'good' publication simply because it wasn't registered; on-going influence of sponsors to not jeopardize the release of a new and potentially profitable product. A more complicated reason may be related to the confidentiality of commercial information: parties are

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hesitant to disclose data that could be viewed as proprietary. Some researchers, who accede to the registration, resist the idea of disclosure of results for a variety of reasons, mostly to do with competition [8]. These are important issues that warrant thorough discussion.

Regardless of the rationale for not registering or for not disclosing outcomes of studies, the fact remains that compulsory pre-trial registration has been accepted by international bodies like the WMA and WHO, by the ICJMR and other leading journal editors, by many in the research community, and by other members of the private and public sector [9]. Further, it has been entered into the policies and, in some cases, the laws of national governments that participate in these forums. And regardless of the reasons for not complying, the result is the same: the public and the profession are being denied the full picture of research that may eventually affect their own research, their clinical as well as their policy decisions, and, not least, their lives and the lives of their families [10, 2]. Clinical trial registration, in this regard, is a public good: it will benefit all, if all participate.

As for those journals that show no evidence of endorsing this policy (i.e., no requirement for a trial registration number, no reference to compliance with the URM in their instructions to authors), we fail to see justification for their actions. While there may be arguments about full disclosure of results, the arguments against registration have largely focused on the impact on small journals and on those published in developing countries: that the added requirements will further delay publication in journals that are understaffed to begin with; or that small journals, hungry for submissions, are in no position to turn down an article because of lack of a registration number [11]. Many of these arguments can be answered by moving the bureaucratic steps to a different level of decision-making (see below) so that no matter where a study originates (and many clinical trials in smaller countries are often a part of a larger multi-center study) it arrives on an editor's desk with a registration number.

The problem with noncompliance is found in other international conventions and regulations, including the International Health Regulations: noncompliance comes with no or little penalty. Journals, editors, even sponsoring institutions may ignore the regulations, either through negligence, ignorance, or willfulness in pursuit of a 'hot' publication and suffer no consequences. Authors get to add the publications to their resumes, universities and medical schools use them to satisfy institutional quality assurance demands, and some research investors are pleased that statistically significant secondary results are positively cited, while negative primary results are either downgraded to a secondary status, or ignored altogether. Researchers who are doing meta-analysis of a topic using available evidence-based research are unwitting accomplices when they publish analysis of only part of the picture.

The authors of the article in this month's journal speculate that raising the awareness among researchers and journal editors might improve registration. That might be enough; a good deal of voluntary participation by public and private stakeholders has already taken place. We agree with the authors' suggestion but would take it further. In order to reduce the bureaucratic burden on all journals, large and small, and to improve uniformity as well as universality in compliance, we would start by requiring that pre-registration of clinical trials *without exception* be a prerequisite for and linked to ethical approval by boards of academic review.

To do this will require educating not only the journal gate-keepers about the importance of requiring and complying with the registration, but also the institutions that are bound by the rules of ethical research. Work will be needed to empower research review boards, chaired or directed by third parties without a vested interest in the outcome of the research, to even-handedly referee compliance and to monitor performance. Penalties for non-compliance at this stage can only come through review and pressure by peers both within and between Universities, medical schools, and other research institutions. Reporting on compliance should be on the agenda of all annual professional meetings where representatives of these institutions gather.

Finally, it is important that institutional review boards, journal editors, and the international research community work together to expand each other's knowledge and ability to solve the problems of implementing this registry. Education of the citizenry on how to use available information is also necessary as they are the ultimate beneficiaries of compulsory registration. It is a public good, and the public's health is at stake.

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