Editorial

Clinical Trials Registration in India: no longer a dream

The prospective registration of clinical trials is no longer a dream in many parts of the world. Editorial initiatives such as the position taken by the International Committee of Medical Journal Editors (ICMJE) that precludes the publication of reports of clinical trials that had not been previously registered in approved clinical trial registers paved the way for this collective endeavour. Efforts by the international community and its representative organisations such as the WHO International Clinical Trials Registry Platform (WHO ICTRP) helped decide elements that would be disclosed at registration (the 20-item dataset), initiate dialogue among stakeholders for overcoming perceived barriers to disclosure of sensitive trial elements, provide a search portal that would link approved clinical trial registers (http://www.who.int/ictrp/search/en/), and will help guide the reporting of clinical trial results. Periodic audits of the process and contents of prospective registration by registries themselves led to a dramatic improvement in compliance with registration requirements. Numerous articles in the lay and scientific press stressing the importance for public good over concerns of competitive disadvantage advanced by those with commercial interests helped shape public and scientific opinion. Efforts from within the pharmaceutical industry also contributed to the process. Legislation left no room for reluctance to be transparent in some parts of the world. Registration of the ICMJE and WHO’s 20-item dataset is now an essential part of the process of initiating clinical trials worldwide. Interest has now shifted to issues related to making trial results publically available.

Why is prospective registration of clinical trials important?
The reasons for these initiatives are also well known to those who have been following this unfolding saga. Prospective registration of clinical trials, by providing a public record of the existence of a trial, its essential elements and key players, will prevent the many unsettling high-profile examples of selective reporting (for example failure to report all adverse events). It will also prevent publication bias and discrepancies in reporting outcomes between trial protocols and published reports. Trial registers are also used by patients and healthcare providers to identify clinical trials they may wish to participate in. They have other potential uses for policy makers and funding agencies, in research priority setting, resource utilisation and capacity building for research, as well as for everyone involved in the informed healthcare decision making process; they provide a summary of necessary evidence that would be missing if one were only to rely on published trial reports, since many trials are never published or only report selected outcomes. Registering clinical trials is therefore considered a scientific and ethical imperative.

Clinical Trial Registration in India: no longer a dream
The dream of clinical trial registration in India became a reality with the launch of the Clinical Trials Registry- India (CTRI; www.ctri.in) on June 20, 2007. Situated and administered out of the National Institute of Medical Statistics at New Delhi, the CTRI forms one of the Primary Registers of the WHO ICTRP’s registry network, and trials in the CTRI will be included in the central repository of the WHO ICTRP Search Portal. The CTRI accepts registration of ongoing and planned clinical trials of any intervention involving human participants conducted in India. It will, however, assign a valid registration number only to trials disclosing meaningful information for all 20 items of the WHO dataset. Registration and access to registered trials are free. Multi-country trials with any recruitment site(s) in India are expected to prospectively register the India-specific details in the CTRI, even if the trial is registered in another register but the trial identification numbers allocated by other registers are also required in the dataset submitted.

The dream of Clinical Trials Registry- India
The CTRI was designed against the stark realities governing the conduct of clinical trials in India. Profit is largely the motive that drives the burgeoning healthcare industry in India (profit-based medicine) and this extends to the conduct of clinical trials as well. Outsourced industry-sponsored trials often use numerous private trial sites with uncertain ethics and doubtful protection of vulnerable participants. Hence, the CTRI requires, in addition to the 20-item dataset, the names of all ethics committees from whom approval has been sought, details of the approval status at the time of registration, a copy of the ethics committee approval letter(s) and a copy of the clearance letter from the Drugs Controller General of India (if applicable). This will complement the initiative of the Indian Council of Medical Research (ICMR) to identify and eventually accredit all ethics committees in India.

Industry-bashing is a popular past-time for many, and industry-sponsored trials are often pilloried in the lay and scientific press. However, it is often not appreciated that investigator-initiated trials also pose problems. Numerous clinical trials of drugs, psychological interventions, devices and surgery are done every year in medical colleges often with insufficient ethical oversight or even valid research designs. These trials are often not reported once the requirements of these submissions or conference attendance is fulfilled. Those that do make it to publication often reveal important deficiencies in reporting requirements that are likely to have been the result of poor trial design, and journal editorial policy and peer review do not necessarily prevent these trials of doubtful validity from achieving the perceived sanctity of published truth. The CTRI therefore included disclosure of crucial elements of validity of a clinical trial, such as methods used to generate the randomisation sequence, conceal allocation and blind both participant and investigator with downloadable explanatory documents; these aimed to educate the investigator, in the hope that it would lead to better conduct and valid reporting of results. Disclosure of these elements is not mandatory as yet.
**From dreams to reality**

If clinical trial registration is to become a dictum in India, then concerted and widespread efforts are required to encourage prospective registration by all concerned, since registration is currently voluntary. Education is an important component of this and the importance of prospective registration and details of registration requirements need to be incorporated into teaching programmes and research methodology courses. Dialogue with drug companies and contract research organisations in India have commenced and should continue to allay unwarranted anxieties. Consumer groups should educate potential trial-conductors on the potential hazards of participating in trials that are not registered in an approved registry. Academic institutions and ethics committees ought to consider clinical trial registration an important part of their mandate for balancing the risks and benefits to the participant. Some have already accepted this mandate and have increased the quality of design of trial protocols in the process. Periodic audits of information disclosed in the CTRI, combined with comparisons of trials approved by the DCGI and independent audits by agencies such as the ICMR on ongoing trials in institutions would help assess the acceptance of trials registration by the research community; naming defaulters would leave them little room for manoeuvre. In the absence of specific legislation concerning prospective registration thus far in India, amending the declaration of Helsinki, and the ICMR’s bioethics guidelines for research in human subjects would help make clinical trial registration a legal and ethical requirement; this is because Schedule Y of the Drugs and Cosmetics Act requires researchers in India to follow these guidelines. Medical journal editors are also important gatekeepers of the validity of published research and since one of the stated goals of the fraternity is to work towards improving the quality of the conduct and publication of research, for the reasons detailed herein, clinical trial registration forms an important component of fulfilling this goal. There have been sporadic calls to encourage medical journal editors to support the ICMJE and WHO ICTRP positions on prospective registration of trials that have been increasing in frequency and some have endorsed the ICMR initiated CTRI. The ICMR and groups of medical journal editors from India have collectively and independently met and discussed the possibility of making necessary the prospective registration of clinical trials as a pre-requisite to consideration for publication of manuscripts submitted to Indian medical journals. Consensus is being sought but concerns of dwindling submissions, were this to be implemented, and potential publication bias whereby good quality but un-registered trials would be rejected by leading Indian journals and published in less accessible overseas or local journals have been voiced. However, the time is ripe for concerted action from the fraternity of Indian medical journal editors to put aside these concerns and endorse the ICMJE position on clinical trial registration as a pre-requisite to publication in all Indian medical journals in the greater interests of public good, scientific credibility and editorial responsibility. Nothing short of this may be tolerated if our design for clinical trial registration is to be realised, our obligation to the trial participant and the Indian public.

**REFERENCES**