COMMENT

Ethics committees and clinical trials registration in India: opportunities, obligations, challenges and solutions

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Abstract

Registering clinical trials is considered an ethical and moral imperative. The launch of the Clinical Trials Registry-India provides opportunities to all in India to fulfil this imperative. The CTRI requires prospective registration, disclosure of all 20 items in the WHO Trial Registration Data Set and proof of ethics and regulatory clearances. Registration in the CTRI is voluntary. However, institutional research ethics committees have obligations. This article reviews these obligations and provides an example of how this can be achieved.

The ongoing worldwide saga of prospective registration of clinical trials entered a new chapter this year with the launch of the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP) search portal in May (http://www.who.int/trialsearch/). This search portal will display the 20-item WHO trials registration dataset of trials registered in primary registers of the WHO ICTRP network of registers. The Clinical Trials Registry-India (CTRI), launched on July 20, 2007, forms one of the primary registers in this network. Data from the CTRI will be included in the WHO search portal (1). These two events herald opportunities and challenges.

Events leading up to trial registration in India

This watershed in the story of clinical trials in India began with the statement from the International Committee of Medical Journal Editors (ICMJE) in 2004 (2). The ICMJE required that all clinical trials (except some Phase I trials) be registered, and their design disclosed, in a publicly available register before enrolling participants. This was a pre-requisite to submission to ICMJE member journals.

The WHO definition of a clinical trial includes Phase I trials. The pharmaceutical industry initially balked at full disclosure for Phase I trials on the grounds that this could threaten the competitive advantage that drives innovation. They proposed delayed disclosure of sensitive items, such as interventions, sample size and outcomes, that could be used by competitors to their advantage (3). However, the tragedy of Parexel's Northwick Park TGN1412 Phase I trial, which had not been available for public review, led to calls by patient advocacy groups for more transparency in the interests of saving lives (4). Subsequently, the ICMJE endorsed the WHO 20-item dataset, the registration of Phase I trials, the WHO ICTRP search portal and the network of primary registers (5, 6).

The challenges of registering trials in India

India has become an attractive destination for outsourced industry-sponsored international clinical trials for various reasons (7). The lack of regulatory jurisdiction over private trial sites and the uneven application of the need for informed consent and proper ethics review have raised concerns about trials conducted in India (8). With profit as the bottom line, exploiting opportunities rather than transparency or the protection of vulnerable populations appears to drive the industry (9).

The requirements of the CTRI

The CTRI will assign a valid registration number only to trials disclosing meaningful information for all 20 items of the WHO dataset. In addition, the CTRI requires 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 (for trials that require this).

These register-specific items, not mandated by the WHO 20-item dataset, provide an opportunity, in the absence of legislation, to ensure prospective registration of clinical trials in India. They may slow the registration process but could be the first step in ridding India of its international reputation for sloppy ethics oversight of research. However registration is voluntary.

Role of ethics committees in registering trials

An example of the role that research ethics committees could play in trials registration is now in place at the Christian Medical College, Vellore, Tamil Nadu. The application form for institutional funding and /or research ethics committee approval was modified to include all the items required by the CTRI. It also includes a declaration, to be signed by all investigators, that the trial would be prospectively registered in the CTRI. Ethics clearance is provisional till a valid CTRI registration number is provided to the ethics committee, along with a copy of the details of CTRI registration. In addition, the office of research will monitor all trials approved by the ethics committee to ensure that valid prospective trial registration has occurred before commencement of the trial. The format for submission of the final report to the ethics committee will also require the CTRI number and, when it becomes available, the WHO ICTRP's Universal Trial Registration Number (3).

Obligations of ethics committees

Prospective registration of clinical trials is considered a scientific and ethical imperative for researchers and trial sponsors (1). Requiring prospective registration can also be considered an ethical imperative for ethics committees since safeguarding the rights of trial participants and weighing risks and benefits are cardinal obligations of any research ethics committee (10).

People participate in trials for personal benefit but also for potential social benefit. Trial registration, by virtue of declaring the presence of a trial and declaring details of the trial protocol, can form the basis for further research. This indelible public record of a trial's existence is necessary as researchers or trial sponsors may seek to circumvent the ICMJE's requirement by publishing their results in journals not endorsing the ICMJE position; or not publishing any results. Registration can also inform future research subjects or patients, enlighten those who plan or fund new proposals (10); and reduce duplication of effort and duplicate publication.

Access to a complete list of ongoing and planned trials is also important for those who search for all trials that are conducted (irrespective of publication status) on a particular topic to include in systematic reviews and meta-analyses.

These potential benefits of any trial are reasons for institutional ethics committees to balance against risks to trial participants, or lack of direct benefit from participation.

Interlinking obligations, guidelines and legislation

The CTRI's requirements will complement the bioethics initiative of the Indian Council of Medical Research (ICMR) to identify and eventually accredit all ethics committees in India (11). Legislation to legally endorse this initiative has been pending in parliament for some time. However, Schedule Y of the Drugs and Cosmetics Act (12) requires researchers to abide by the World Medical Association's Declaration of Helsinki (13), and the ICMR's ethical guidelines for research (11). Prospective trial registration is not an explicit requirement in the WMA Declaration or the ICMR guidelines. The WHO-ICTRP has recommended to the WMA an amendment of clause 16 to make prospective registration in a publicly accessible register explicit in the proposed revisions of the Declaration of Helsinki. The ICMR ethical guidelines also need to be revised to include endorsement of prospective registration in the CTRI.

Since Schedule Y requires researchers to abide by the ICMR guidelines (12), regulators and ethics committees would then be obliged to support trial registration as a legal as well as an ethical requirement.

References

1. World Health Organization. International Clinical Trials Registry Platform (ICTRP). List of Registers. [cited 2007 10 Aug] Available from: http://www.who.int/ictrp/network/list_registers/en/index.html
2. DeAngelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *N Engl J Med* 2004;351:1250.
3. Tharyan P. The WHO international clinical trials registry platform and the Indian clinical trials register. *Natl Med J India* 2006; 19:161-4.
4. Goodyear M. Learning from the TGN1412 trial. *BMJ* 2006;332:677-8.
5. DeAngelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors. *Lancet* 2005;365:1827-9.
6. Laine C, Horton R, DeAngelis CD, Drazen JM, Frizelle FA, Godlee F, et al. Clinical trial registration - looking back and moving ahead *Lancet* 2007;369:1909-11.
7. Nundy S, Gulhati CM. A new colonialism? Conducting clinical trials in India. *N Engl J Med* 2005;352:1633-6.
8. Gulhati CM. Needed: closer scrutiny of clinical trials. *Indian J Med Ethics* 2004;1:4-5.
9. Tharyan P. Whose trial is it anyway? Reflections on morality, double standards, uncertainty and criticism in international collaborative health research. *Monash Bioeth Rev* 2006; 25(4):53-68.
10. Levin LA, Palmer JG. Institutional review boards should require clinical trial registration. *Arch Intern Med* 2007;167:1576-80.
11. Indian Council of Medical Research. *Ethical guidelines for biomedical research on human participants*. New Delhi: Indian Council of Medical Research; 2006.
12. Ministry of Health and Family Welfare. Drugs and Cosmetics Act and Rules. Central Drugs Standard Control Organization. New Delhi; 2005. [Cited 2007 Aug 16] Available from: http://www.cdsco.nic.in/html/Copy%20of%201.%20D&CAct121.pdf
13. World Medical Association. Declaration of Helsinki. *Ethical principles for medical research involving human subjects*. Adopted by the WMA in 1964 and last amended in 2000. [Cited 2007 Aug 16]. Available from: http://www.wma.net/e/policy/b3.htm

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