Review Article

Clinical Trials Registry – India: Redefining the conduct of clinical trials

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Introduction

Recently, there has been growing concern about the selective publication of clinical trial results[1,2] and its consequences on the practice of "evidence-based medicine." Selective reporting of clinical trials results leads to bias in published clinical trial literature in favor of positive or promising results. This contention has been convincingly demonstrated by Simes as early as 1986.[3] He reported that a pooled analysis of *published clinical trials* demonstrates a significant survival advantage for advanced ovarian cancer given combination chemotherapy (versus initial alkylating agent, $P = 0.02$). However, no significant difference in survival is demonstrated based on a pooled analysis of *registered* trials ($P = 0.25$). Similarly, for multiple myeloma patients, whereas pooled analysis of registered trials also shows a survival benefit for patients receiving combination chemotherapy, the estimated magnitude of the benefit is reduced. These data underscore the propensity for misleading information being generated from data analysis of only published clinical trial literature. The most effective antidote to this problem may be through registration of all clinical trials and making their results available publicly. Registration of clinical trials offers other benefits as well, such as safeguarding of patient interests and ensuring greater transparency, accountability and accessibility of clinical trials whereas at the same time also helping to raise the standard of research.

World Scenario

The need for registration of clinical trials has long been felt at the global level. In November 2004 at the Ministerial Summit on Health Research, all participants called for action by all major stakeholders, facilitated by the World Health Organization (WHO) secretariat, to establish a platform for linking of all international clinical trials registries to ensure a single point of access and unambiguous identification of trials.[4] A number of clinical trial registries were already in place, but mostly in developed countries, and none were truly comprehensive. Hence, the WHO took up the lead, in 2005, to establish the International Clinical Trials Registry Platform (ICTRP), a one-stop search portal for identification of trials fed from existing registers and provide a unique identification number for clinical trials from certified registers that meet standard criteria for the exchange of essential trial data, such as disclosing 20 key details of the trial before the enrollment of the first patient.[5] Further, a commitment has also been made by the International Committee of Medical Journal Editors (ICMJE) that registration of clinical trials is a prerequisite for consideration of clinical trial data publication.[6]

Relevance in the Indian Context

The issue of clinical trial registration is of particular relevance in our country as India has become the preferred hub for the conduct of clinical trials. According to estimates of a global consultancy, McKinsey and Co., by 2010 global pharma majors would be spending up to $1.5 billion just for clinical trials in India. A Rabobank India report says that India has the largest pool of naïve patients in many diseases, including cancer and diabetes. The report also highlights India's biggest advantage as the low cost. For instance, trials for a standard drug in the United States can cost up to $150 million, whereas a trial in India is conducted for nearly half that amount.[7]

The availability of specialty hospitals with state of the art facilities manned by a significant number of GCP-trained clinicians and a large English proficient work force has all added to the charm of India as a clinical trial hub.

However, on the flip side, there have been growing concerns and fears that due to vested interests, negative trial results are often not brought to the notice of the general public and physicians. The Vioxx controversy[8] and reports of unethical clinical trials being conducted in India without proper clearance from relevant authorities or proper toxicity studies[9] have brought to the forefront the urgent need for registration of all clinical trials, including those conducted in India.

It is with this background that the Clinical Trials Registry – India (CTRI) has been set up at the National Institute of Medical Statistics, ICMR, New Delhi. The CTRI is an online and freely searchable platform wherein clinical trials being conducted in India may be registered while declaring certain information regarding the trial (as defined by the CTRI registration data set - Table 1). These details of registered trials are freely available and accessible at the CTRI site (www.ctri.in).

Table 1: Registration data set of the CTRI (to be filled and submitted online only)

Public Title of Study*
Scientific Title of Study* and Trial Acronym, if any
Secondary IDs, if any
Principal Investigator's or Overall Trial Coordinator's (in case of multicentre trial) Name and Address
Contact Person (Scientific Query)
Contact Person (Public Query)
Funding Source/s
Primary Sponsor
Secondary Sponsor
Name of Ethics Committee and Approval Status*
Regulatory Clearance Obtained from DCGI*
Date of First Enrollment
Estimated Duration of Trial
Target Sample Size
Health Condition/Problem Studied
Intervention and Comparator Agent
Key Inclusion/Exclusion Criteria
Primary Outcome/s
Secondary Outcome/s
Countries of Recruitment
Site/s of study
Status of Trial*
Phase of Trial*
Study Type
Brief Summary
Method of Generating Randomization Sequence
Method of Allocation Concealment
Blinding and Masking

Fields marked with asterisk* are mandatory for registration. For more information visit us on www.ctri.in

Goal and Objectives of the Registry

The main objectives of the registry are to establish a public record system by registering all clinical trials on health products that are drugs, devices, vaccines and herbal drugs. Further, it also aims to create a more complete, authentic, public and readily available data of all ongoing and completed clinical trials and to provide a corrective system against "positive result bias" and "selective reporting" of research results to peer review publication. In addition, the vision is to increase awareness and accountability of all the participants of the clinical trials and also for public access to promote training, assistance and advocacy for clinical trials by creating database and modules of study for various aspects of clinical trials and their registration.

The specific goal of setting up a clinical trial registry would ensure that all clinical trials conducted in India are registered and publicly declared and identifiable. Further, a minimum set of information of all clinical trials will be freely available to physicians, health researchers, academicians, pharmaceutical industries as well as to the common man, which will increase public trust in the conduct of clinical research.

The CTRI

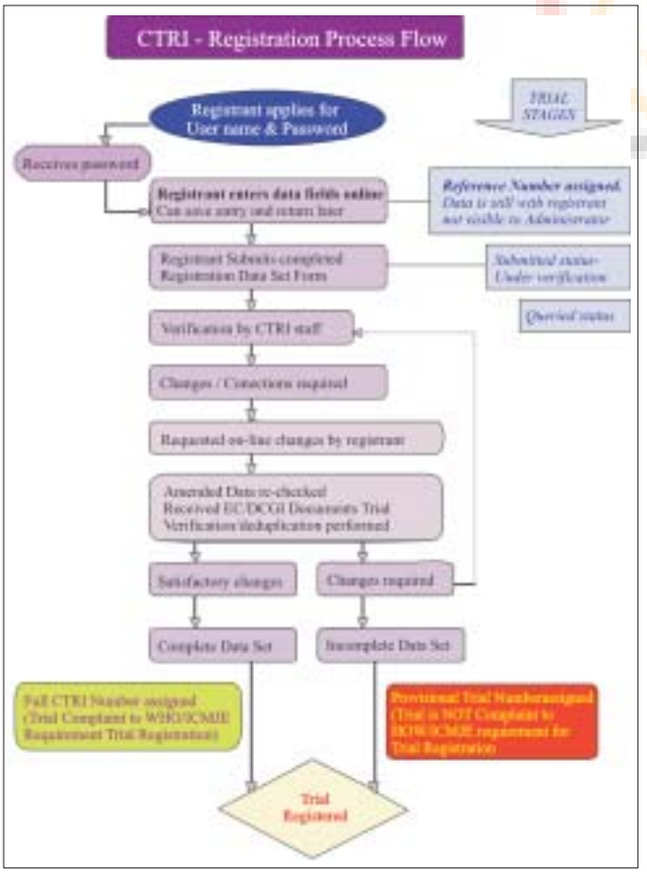
The CTRI is a not-for-profit organization and the registry has been designed in a way that it will be able to collect all items of the Registration Data Set, link it to WHO's ICTRP and perform quality assurance on submitted entries. The registry will have a mechanism in place for obtaining updated data as well as performing deduplication of submitted trials. Deduplication is the process of identifying whether two sets of data belong to the same trial or belong to two different unique trials.

Process of trial registration in CTRI: All clinical trials being conducted in India are expected to be registered through an online process in the CTRI. Trialists first need to register as a user in the CTRI. Subsequently, on receipt of username and password, trialists are required to submit details of the trial according to the trial registration data set [Table 1].

Although it had been proposed that a Universal Trial Reference Number (UTRN) would have to be acquired from the ICTRP before registration with a primary registry, this process is not yet functional. Hence, currently, a temporary UTRN is being automatically generated and assigned by the CTRI software application to any trial that is being processed for submission.

As per the requirements of the WHO ICTRP, all member registers must collect all items of the 20 points. The WHO further encourages additional data set items as per the needs of a particular registry. In this regard, a few additional items have been recommended by the Technical Advisory Committee to be adopted for the CTRI [Table 1].

Registrants have the facility to fill up the data set, in part or full, according to their individual convenience by clicking on the save button and a reference number is assigned (REFCTRI), which is used in all future correspondence regarding the trial. Once the trial is submitted, the CTRI staff verifies and validates the details. In case of any ambiguity, the trial details are sent back to the trialist for further modifications/ clarifications. It is only after the completion of these formalities and receipt of DCGI/EC documents that a trial is registered and assigned a registration number. If all the WHO fields are filled, a full CTRI registration number (CTRI) that fulfills WHO/ICMJE requirements is assigned. However, incomplete entries are assigned a provisional registration number (PROVCTRI), which is not sufficient for journals who endorse the ICMJE recommendations [Flow chart].



Current Status of the CTRI

The CTRI was formally launched on the 20th of July, 2007, and awareness regarding the registry has gained momentum, as evidenced by the number of hits received by the CTRI site having crossed the 4500 mark. Further, till the 31st of March, 2008, a total of 179 users had been registered, out of which 98 were from the academia (institutions and hospitals), 47 from the pharmaceutical industry and 34 from the contract research organizations [Figures 1 and 2]. Further, 29 trials have been fully registered, 18 trials are pending with the respective registrants for various modifications/clarifications, whereas 12 trials are pending with the Administrator, awaiting EC/DCGI approval documents [Figure 3]. It is interesting to note that while the registered trials are on a wide range of health conditions such as heart disease, skin disorders, dentistry and diabetes, 10 trials are currently being conducted on cancer patients. In addition, three more trials on cancer have been received and are likely to be registered very soon.

While it is the mandate of the WHO to register clinical

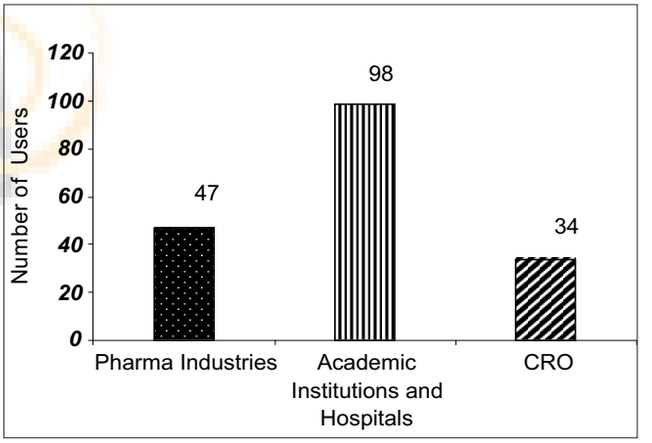


Figure 1: Category of registered users

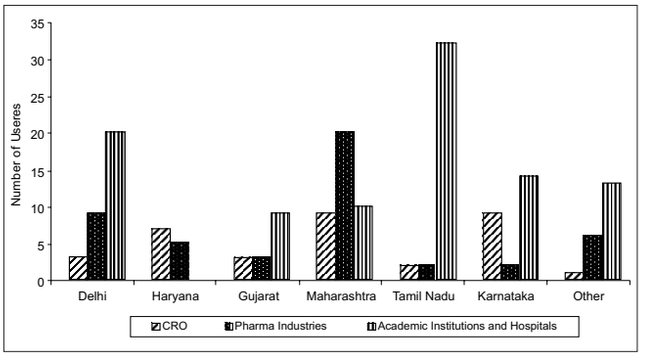


Figure 2: State-wise breakup of registered users

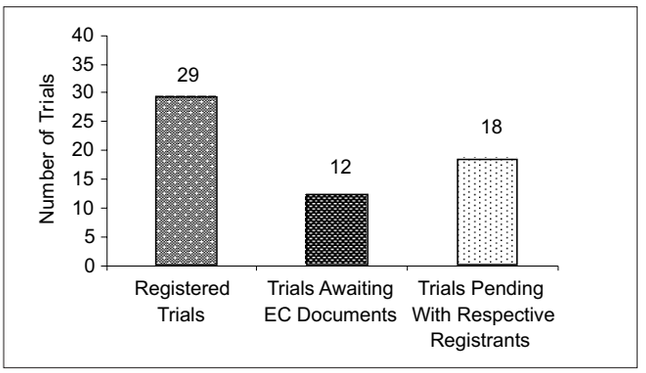


Figure 3: Status of trials submitted to the CTRI

trials prospectively, i.e. before the enrollment of the first patient, currently, in the CTRI, ongoing trials, i.e. where patient recruitment has started are also being registered. However, data of only prospectively registered trials will be linked with the WHO's search portal, the ICTRP.

Advocacy and Consensus Building of CTRI

Several meetings with various stakeholders have been held in an effort to generate consensus as well as to spread awareness regarding the imperative need for clinical trial registration.

A regional meeting was organized at the NIRRH, Mumbai, in September 2007 (from where the maximum numbers of users have registered) to familiarize them with the concept and working of the CTRI. Further, a meeting was held at the ICMR in October 2007 with the editors of Biomedical Journals of India to garner their support and commitment to the cause of CTRI and make trial registration a prerequisite for considering a trial for publication in Indian journals as well. The editors gave a positive reaction to the initiative and are in the process of chalking out a program for generating awareness regarding need for clinical trial registration before imposing it on the research community. Advocacy and dissemination of the need for clinical trial registration and the CTRI was taken further by presentations by various scientists involved in the registry at numerous conferences, both within and outside the country.

Efforts are also underway to include and involve the various Ethics Committees in this venture, and as a positive sign, the Ethics Committee of CMC Vellore has made clinical trials registration a prerequisite for approval of a clinical trial protocol. We are hopeful that in the near future many more ECs will follow suit with the one objective of ensuring that research in medical science keeps the interest of the patient as its first priority. We have no doubt that all clinical trial researchers in India will appreciate this venture and join in with no holds barred.

Acknowledgments

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