CME article

Clinical Trial Registration: What do we need to know?

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Abstract

Trial registration has become an important part of clinical trials and various databases exist across the world. In India, the Clinical Trial Registry India (CTRI) was established in 2007 to promote registration of clinical trials in the country. This initiative which was part of a move to promote transparency in clinical trials has now become a requirement for publication of clinical trials across most journals. This article discusses the importance of clinical trial registration and describes the steps required to complete the registration of a clinical trial in the CTRI database.

Keywords: Clinical trials, Clinical trial registry India, Randomized controlled trials, Trial registration.

Introduction

Clinical trials are often used to compare a new form of intervention with a standard intervention, or to a placebo intervention, or with no intervention. Such trials have led to important breakthroughs in healthcare and have come to play an important role in evidence based clinical practice. Despite being a scientifically robust method for evaluating interventions, clinical trials have been under the scanner for the past three decades for problems such as selective reporting and publication bias.[1] It was being observed that conclusions drawn from trials that registered their protocols prospectively in a registry were different from those drawn from trials that were not prospectively registered in registries.[2] To overcome this limitation in conduct and reporting of clinical trials, regulatory bodies started laying guidelines for prospective registration of the clinical trial protocols.[3] Currently, it is mandatory to prospectively register a clinical trial in a publicly accessible registry and provide relevant details about the clinical trial. This article will discuss the various aspects of clinical trial registration and provide information on the various components required to complete the registration of a trial.

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What is clinical trial registration?

World Health Organization (WHO) regards trial registration as the 'publication of an internationally-agreed set of information about the design, conduct and administration of clinical trials'.[4] These details are published on a publicly-accessible website which serves as an interactive platform and catalog for registered clinical trials. These sites which house clinical trials are hosted by various organisations across the world (*Table 1*). Information from all these websites are compiled by the WHO International Clinical Trial Registry Platform (ICTRP). This provides a single searching database for on-going trials across all trial registry databases from across the world. Currently ICTRP has 14 primary registries as its participating members and anyone wanting to know about trials registered in the 14 registries can search for the trials through ICTRP web portal. The 14 primary registries, their country of origin/geographical coverage and links to their website are summarised in *Table 1*.

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Table 1: Primary and partner* registries participating in International Clinical Trials Registry Platform (ICTRP)

Trial registry	Website	Country/Region
Primary registries of ICTRP		
Australian New Zealand Clinical Trials Registry (ANZCTR)	http://www.anzctr.org.au/	Australia and New Zealand
Brazilian Clinical Trials Registry (ReBec)	http://www.ensaiosclinicos.gov.br/	Brazil
Chinese Clinical Trial Registry (ChiCTR)	www.chictr.org/	China
Clinical Research Information Service (CRiS)	https://cris.nih.go.kr/cris/en/use_guide/cris_introduce.jsp	Republic of Korea
ClinicalTrials.gov	https://clinicaltrials.gov/	USA
Clinical Trials Registry - India (CTRI)	www.ctri.nic.in	India
Cuban Public Registry of Clinical Trials (RPCEC)	http://registroclinico.sld.cu/en/home	Cuba
EU Clinical Trials Register (EU-CTR)	https://www.clinicaltrialsregister.eu	European Union
German Clinical Trials Register (DRKS)	https://www.germanctr.de/	Germany
Iranian Registry of Clinical Trials (IRCT)	www.irct.ir	Iran
ISRCTN.org	www.isrctn.org	UK
Japan Primary Registries Network (JPRN)**	http://rctportal.niph.go.jp/link.html	Japan
Thai Clinical Trials Registry (TCTR)	www.clinicaltrials.in.th/	Thailand
The Netherlands National Trial Register (NTR)	www.trialregister.nl	Netherlands
Pan African Clinical Trial Registry (PACTR)	www.pactr.org	Africa
Sri Lanka Clinical Trials Registry (SLCTR)	http://www.slctr.lk	Sri Lanka
Partner registries of ICTRP		
Clinical Trial Registry of the University Medical Center Freiburg Affiliated registry	http://zksinternet.ukl.uni-freiburg.de/ukfreg/	Germany
DeReG - German Registry for Somatic Gene-Transfer Trials Affiliated registry	http://www.dereg.de/	Germany
Centre for Clinical Trials, Clinical Trials Registry – Chinese University of Hong Kong	http://www.cct.cuhk.edu.hk/cctwebsite/default.aspx	China

* Partner registries do not meet the requirements of the ICMJE. Partner registries are included on the database of a Primary Registry

**This is composed of three registries (viz., University Hospital Medical Information Network, Japan Pharmaceutical Information Center - Clinical Trials Information and Japan Medical Association - Center for Clinical Trials)

Source: http://www.who.int/ictrp/network/en/ (accessed on July 4th, 2015)

The mandatory requirement for trial registration does not differentiate researchers on the basis of nationality, institution, seniority, funding status and the like. In essence, all clinical trials being conducted on human participants (including those being conducted as part of undergraduate/postgraduate student projects) need to be prospectively registered.

What type of clinical trials should be registered?

The definition of a clinical trial has undergone changes over the last decade. Most recently the National Institute of Health (NIH), USA, revised its definition of clinical trial as 'a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes'.[5] All clinical studies meeting the present definition of clinical trial should be prospectively registered in a publicly accessible registry. For the purpose of greater clarity, NIH has defined the terms 'intervention' and 'biomedical or behavioural outcome' in detail. An intervention is defined as 'manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioural processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (*e.g.*, surgical techniques); delivery systems (*e.g.*, telemedicine, face-to-face interviews); strategies to change health-related behaviour (*e.g.*, diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.' And health-related biomedical or behavioural outcome is defined as 'the pre-specified

goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (*e.g.*, mood management intervention for smokers; *e.g.*, reading comprehension and /or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and, positive or negative changes to quality of life.'

However, it must be noted that clinical trials where the intervention is directed at the therapist and therapists rather than patients are assigned to the intervention groups (*e.g.*, a trial evaluating the efficacy of an education intervention designed to improve health professionals' knowledge about a particular condition) are not required to be registered. Though this type of studies may be conducted in the form of a randomised clinical trials, they measure outcomes at healthcare professional level rather than at patient level and hence are exempted from trial registration.[6]

What are the advantages of registering a clinical trial?

Registering the trial has numerous advantages to the researcher, stake holders and most importantly to the participants in the trial. As a trial protocol is registered at the beginning of a study, subsequent publications resulting from the registered trials could be scrutinised for their adherence to protocol. This process greatly enhances the accountability of researchers engaged in clinical trials. In addition to reducing selective reporting of results and publication bias, prospective registration of clinical trials has a few other advantages.[7] In addition, this also provides information about ongoing or registered trials which helps researchers identify similar studies and work towards collaborative research. This platform further provides funding bodies crucial information to help minimise the scope of duplication of research, thus enabling judicious use of funds. From a public perspective, trial participants and volunteers are able to identify studies that they would be interested to participate in. This will help them make informed decisions about participating in a clinical trial.

Where can clinical trials be registered?

To facilitate registration of clinical trials, regulatory bodies in many countries have created online trial registries that allow investigators to prospectively upload information about their trials in a pre-defined format. The NIH created the first publically accessible clinical trial registry in February 2000 (accessed through ClinicalTrials.Gov).[7,8] Subsequently many countries have set up their own trial registries and have made it compulsory for researchers to prospectively register their trials in their National registries. A few registries like the Pan African Clinical Trial Registry or EU Clinical Trials Register cater to trial registration needs of researchers from among a group of nations. Researchers from Countries that do not have a National trial registry can prospectively register their trials in any publically accessible trial registry. Clinicaltrials.gov, maintained by NIH is by far the most commonly used trial registry and as of 24th June 2015, the registry holds records of 35,847 studies of which about 41% studies are from the US, 53% studies from non-US countries and the remaining are from studies conducted in both US and Non-US locations.[8,9]

In India, Clinical Trials Registry – India (CTRI), which is the joint venture of the Indian Council of Medical Research and the National Institute for Medical Statistics, was launched on June 20, 2007 and from June 2009, prospective registration of clinical trials became a mandatory requirement of Drugs Controller General India (DCGI).[10,11] As per DCGI regulations on trial registration, even multinational clinical trials in which participants from India are recruited needs to be prospectively registered in CTRI.[12] Trials registered in CTRI conform to WHO's trial registry criteria for content, quality and validity, accessibility, unique identification, and technical capacity; and can be searched through WHO ICTRP portal.[4]

Table 2: Components of the CTRI dataset required for registration of clinical trial

No.	Component	Description
1.	Public title of study	Study title that can be understood by the public or lay person
2.	Scientific title of the study and acronym (if any)	The scientific title
3.	Secondary IDs	If there is any other trial registration ID
4.	Principal investigator's (PI) name and address	The main trial investigator's contact details
5.	Contact person for scientific query	This will be contact person for any scientific query
6.	Contact person for public query	This will be the contact details for the person who is to be contacted for public queries
7.	Source of mentor or material support	This should include details of the source of financial support (e.g., funding agency, hospital, company)
8.	Primary sponsor	This should include details of the organization or individual providing financial support for the research "In investigator initiated trials, the principal investigator is the primary sponsor, though the affiliated institution may be the main source of funding, and acknowledged under "Source/s of Monetary or Material Support"."
9.	Secondary sponsor	Details of those assisting the primary sponsor
10.	Countries of recruitment	This provides information on the countries where the recruitment will occur
11.	Sites of study	This includes all the sites and the respective center PI within India participating in the trial
12.	Name of Ethics Committee and approval status	
13.	Regulatory clearance obtained from DCGI	This is important for all pharmacological trials. Note: this may not be relevant to most respiratory therapy interventions unless there is a pharmacological intervention
14.	Health condition/problem studied	This should describe the particular condition being studied
15.	Study type	Describes the type of study (i.e., interventional trial or observational study)
16.	Intervention and comparator agent	Describes in detail the proposed intervention and against what it is being compared (e.g., CPAP versus O2 therapy)
17.	Inclusion and exclusion criteria	Should describe in detail the specified criteria for inclusion into the clinical trial
18.	Method of generation randomization sequence	This describes the method used to generate a random sequence, if it is used (e.,g., lottery method, random number table, computer generated randomization etc.)
19.	Method of allocation concealment	This describes how allocation of the patients into the randomized groups was concealed from the investigator and participant (e.g., sequentially numbered opaque sealed envelopes etc)
20.	Blinding/masking	This describes how the assessor or patient blinding was done*
21.	Primary outcome	This describes the main outcome of the clinical trial with the time points at which they are being evaluated or assessed
22.	Secondary outcome measure	This describes the secondary outcomes of the clinical trials with the time points at which they are being evaluated or assessed
23.	Target sample size	This should mention the pre-determined sample size estimated for the clinical trial. If it is an international, multicentric study, details on the number of participants being recruited globally and from India should be mentioned.
24.	Phase of trial	This should describe in which phase the current clinical trial is (i.e., Phase I, II, III or IV)* An option of 'Not applicable' is also available to the PI
25.	Date of first enrollment	This should clearly state when the first participant is expected to be enrolled
26.	Estimated duration of trial	The expected duration of the clinical trial should be mentioned as per protocol
27.	Recruitment status of trial	This provides information on the current recruiting status of the trial (i.e., not yet recruiting, open to recruitment, suspended, completed, closed to recruitment or terminated). This will need to be updated by the PI
28.	Brief summary	This includes a brief summary of the entire research being proposed
29.	Publication details	Details on publications from the research being registered can be updated on a regular basis by the PI

*This may not always be possible in respiratory therapy driven clinical trials

Appropriate ethical approval is a prerequisite for registering a trial in CTRI and it is the responsibility of the principal investigator to ensure all requirements for trail registration are met and the trial registered prospectively in CTRI. The information required for registering a trial in CTRI is summarised in Table 2. Once the required datasets are submitted through CTRI portal, the information is screened by an administrative staff at CTRI. Queries, if any will be reverted back to the submitting investigator. At this point, there is a temporary number issued. Once the entire submission has been verified and checked for accuracy, the trial is registered and the investigator receives a specific trial registration number. The registration number is unique to the registered trial and can be used to access information about the trial from anywhere in the world either through CTRI web portal or through ICTRP search portal. This trial registration number is unique to the registered clinical trial and is required to be entered while submitting manuscripts for publication in various peer reviewed, indexed journals.

Who can ensure trial registration?

WHO ICTRP states that "the registration of all interventional trials is a scientific, ethical and moral responsibility".[4] It is therefore the responsibility of the principal investigators or research supervisors (in cases of student projects) to ensure prospective registration of their clinical trials. In those instances where researchers do not register their trials, the onus then lies with the journals, institutions, funding agencies and regulatory bodies. Though NIH made prospective registration of clinical trial mandatory in 2000, the process of registration got a major thrust only when International Committee of Medical Journal Editors (ICMJE) made prospective registration of clinical trials as a mandatory criterion for consideration for publication of clinical trial results in their member journals in 2005.[13] Currently most funding agencies require details of trial registration for considering research funding applications. In concordance with the research community worldwide, many steps are being taken in India to ensure prospective trial registration. Key initiatives include setting up of CTRI in compliance with WHO ICTRP requirements; DCGI making it mandatory for all trials conducted in India to be prospectively registered in CTRI; funding agencies like Indian Council of Medical Research making it mandatory for trials funded by them to be registered in CTRI and a few groups of Indian journal editors and publishers making it mandatory for providing trial registration number for the article to be considered for publication in their journals.

Despite such efforts, not all trials are being registered. This has been possible because not all journals have made trial registration a mandatory requirement. It is in circumstances like these that institutions can play a major role. Institutions are better placed to ensure that all trials being conducted by their staff are being prospectively registered. Journal editors also have a major responsibility to ensure adherence to trial registration requirements prior to submission of clinical trials. If all journal editors strictly enforce trial registration requirements, there will be greater adherence to prospective clinical trial registration.

Summary

Registration of clinical trials is important to advance transparency in clinical research. CTRI provides Indian researchers with a platform for registering their clinical trials prospectively while allowing others working in similar areas to collaborate in research. Ensuring registration of all clinical trials is the responsibility of the researcher along with emphasis from journal editors and institutional research boards. There continues to remain challenges in implementing clinical trial registration across all medical disciplines. However, small steps made by educating students and early career researchers on this key area will help promote awareness about trial registration and thereby promote greater registration of clinical trials.

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