JOURNAL OF SOCIETY OF INDIAN PHYSIOTHERAPISTS
ISSN (PRINT): 2456-7787

Research Information

Clinical Trial Registration: A Step towards Transparency and Accountability

Sundar Kumar Veluswamy[1], Abraham Samuel Babu[2]

[1]Assistant Professor, Department of Physiotherapy, M S Ramaiah Medical College, Bangalore

[2]Assistant Professor, Department of Physiotherapy, School of Allied Health Sciences, Manipal University

Corresponding Address: Dr. Sundar Kumar Veluswamy, Assistant Professor, Department of Physiotherapy, M S Ramaiah Medical College, Bangalore; Email- sundark94@gmail.com, sundar.kumar@msrmc.ac.in

Abstract: Clinical trials registration has been advocated for improving transparency and reducing publication bias in clinical trials. Prospective registration of clinical trial in Clinical Trial Registry India (CTRI) is a mandatory requirement in India and it is the obligation of every researcher and institution to ensure that all clinical trials in their institute are prospectively registered in CTRI. Awareness of trial registration among Indian physiotherapists has been low. This narrative review attempts to summarize the importance of clinical trial registration and the process of clinical registration in CTRI and thereby improve awareness of trial registration among Indian physiotherapists.

Key words: Trials, Ethics, CTRI, Physiotherapy, Research.

Introduction

Clinical trials are essential for improving and advancing healthcare.[1] They are intended to assist in determining if a new intervention is effective and safe. Clinical trials are also used to compare interventions or approaches for different diseases and populations. Policy makers use results of clinical trials to frame health policies and prioritise resource allocation. However, only about 50% of clinical trials are reported in scientific publications.[2] Favourable outcomes are more likely to be reported from a given study than unfavourable outcomes (selective outcome reporting).[3] Similarly, studies with positive results are reported to a greater extent than studies with negative results (publication bias). Both these factors (i.e., selective outcome reporting and publication bias) undermine the importance given to clinical trials in the evidence hierarchy. Prospective registration of clinical trial protocols in a publically accessible register has been propagated as a solution to improve transparency in the conduct and reporting of clinical trials.[4,5]

Clinical Trial Registration

Clinical trial registration is the process of 'publication of an internationally agreed set of information about the design, conduct and administration of clinical trials' in a publically accessible register.[6] For a clinical trial to be considered as fully registered, International Clinical Trials Registry Platform (ICTRP), hosted by World Health Organisation (WHO) has prepared a 20-item trial registration dataset that contains the minimum amount of trial information that must appear in a register.[7] Clinical trial registration can be accomplished by providing the required details in one of the 14 primary registries in the World Health Organisation (WHO) Registry Network,[8] or in an International Committee of Medical Journal Editors (ICMJE) approved registry.[9] Clinical Trials Registry- India (CTRI) is part of the WHO registry network and is the primary registry for all clinical trials in India.[10]

Clinical trial registration serves many purposes for various groups.[11] It improves transparency in clinical research and reduces the scope of publication bias; allows for efficient allocation of research funds; helps institutional review boards decide on the appropriateness of a trial; provides

required details to potential participants and referring clinicians; and helps editors and reviewers understand the context of study and raise relevant questions to authors on the basis of information provided during trial registration. Over all, the process of trial registration benefits, patients, general public, institutional review boards, journal editors, research community, funding agencies, and policy makers in improving the quality and accuracy of information generated from clinical trials. Hence, ICTRP considers clinical trial registration to be a "scientific, ethical and moral responsibility" of the researchers.[6]

What type of studies should be registered?

For the purpose of registration: ICTRP defines a clinical trial as 'Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Clinical trials may also be referred to as interventional trials. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc. This definition includes Phase I to Phase IV trials.'[6]

Interventions include use of drugs; instruments and devices (like various physiotherapy modalities, mulligans belt, taping, elastic bands); different treatment techniques (like mobilization, PNF, NDT); health related behaviour change strategies (like health education, diet and exercise advice, behavioural counselling); delivery systems (like hospital, community, individual, group, tele-rehab); and preventive and diagnostic strategies. In essence, all research studies prospectively assigning participants to interventions for modifying health-related biomedical or behavioural outcomes(irrespective of randomized or non-randomized design) are considered clinical trials and hence, should be registered.[6,12] Precise definitions of common terms such as prospective assignment, intervention and outcomes are provided in Table 1.

Despite guidelines by ICTRP, ICMJE and CTRI for trial registration, ambiguity still exists among physiotherapists regarding types of studies that need to be registered. To clear the ambiguity, 'Physical Therapy' Journal issued an editorial[13] adopting ICMJE's policy of trial registration

Table 1: Definition of Keys Terms Related to Clinical Trials*

S. No	Term	Definition
1	Clinical Trial	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 behavioural outcomes.
2	Prospective Assignment	A pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.
3	Intervention	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.
4	Health-related Biomedical or Behavioural Outcome	A pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioural status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neuro developmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviours; and, positive or negative changes to quality of life.

*The listed definitions are based on information provided in the NIH webpage on Clinical Research Policy and was accessed on 25th Aug 2016 from http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/clinical-research-policy/clinical-trials

which states that: 'If the purpose of the trial is to examine the effect of the provider intervention on the health outcomes of the providers' patients, then investigators should register the trial. If the purpose is to examine the effect only on the providers (for example, provider knowledge or attitudes), then registration is not necessary.'

According to the Physical Therapy Journal editorial, clinical trials that assign therapists and not patients to intervention groups (e.g., a trial evaluating the effects of a training program on skill or knowledge of the therapists) are not required to be registered.

How to register clinical trials in India?

Clinical trials in India are regulated by Drugs Controller General (India) (DCGI) and as per its directive in June 2009, all clinical trials being conducted in India should be registered in CTRI before enrolment of the first participant.[10] This is a mandatory requirement for all, irrespective of health discipline, designation, seniority, institutional affiliation, funding status or nationality, to conduct clinical trials in India. This applies even to research conducted in India as part of multi-national trials or undergraduate/postgraduate student projects.

It is the primary responsibility of the principal investigator to ensure registration of trial details in CTRI. For multi-nationals trials that have been registered in other WHO or ICMJE approved registries, the Indian principal investigator should register the trial details in CTRI. For student dissertations, the student or the guide can register the trials.

A new investigator needs to register in the CTRI website's registration page (http://ctri.nic.in/Clinicaltrials/app_register.php) by providing the required details. The applicant is required to provide details of a person who can verify the profile of a new applicant. The verifier needs to be from the same institution as the new applicant and can be head of the department, a senior colleague or the guide. Once registration is approved, the applicant should log-in using his credentials and submit the required details of the proposed clinical trial (Table 2). A soft copy of a valid ethical approval letter is

Table 2. CTRI Dataset*

S. No	Dataset Item	S. No	Dataset Item
1	Public title of study	2	Scientific title of study ; Acronym, if any
3	Secondary IDs, if any	4	Principal Investigator's name and address
5	Contact for Scientific Queries	6	Contact for Public Queries
7	Source(s) of Monetary or Material Support	8	Primary Sponsor
9	Secondary Sponsor(s)	10	Countries of Recruitment
11	Site/s of study	12	Name of Ethics Committee and approval status
13	Regulatory clearance obtained from DCGI	14	Health Condition(s) or Problem(s) Studied
15	Study Type	16	Intervention and comparator agent
17	Inclusion and Exclusion Criteria	18	Method of generating randomization sequence
19	Method of allocation concealment	20	Blinding/masking
21	Primary Outcome(s)	22	Secondary Outcomes
23	Target Sample Size	24	Phase of trial
25	Date of First Enrolment	26	Estimated duration of trial
27	Recruitment Status	28	Brief Summary

* Detailed descriptions of the dataset items are available for download in the CTRI website

mandatory for registering a trial. Once the details are submitted, a reference number is provided and dataset reviewed for completeness by the CTRI office. The investigator receives a mail for any questions raised during the review process. The investigator needs to login using his credentials and reply to the questions raised. If all details are reviewed by CTRI and found to be in order, the investigator receives a unique CTRI ID for the trial and the trial is considered registered. Once registered, details about the trail can be accessed from anywhere in the world using CTRI or ICTRP search portals. Investigators are usually required to submit the CTRI registration details of a trial to institutional ethics committees, government funding bodies to which the investigator is applying for support, and to journals during submission of manuscript based on results of the trial.

CTRI conducts e-learning modules to familiarise new registrants with the registration process. The training program can be accessed from the following link: (http://14.139.60.56:8079/ctri/). Anecdotal experiences suggest CTRI registration to be a time consuming process and can take anywhere between 4-16 weeks. Student projects have generally taken longer to be registered than other studies. Hence investigators should account for the delay in registration and begin the process at the earliest possible time.

Challenges

As of 5th September 2016, there are 7235 clinical trials registered in CTRI out which only 169 are related to physiotherapy. A previous study indicated low awareness (39 %) about trial registration and CTRI among post graduate physiotherapists in India.[14] Despite efforts from leading physiotherapy journal editors, reporting of trial registration details even in Medline indexed physiotherapy journals have remained low(29%).[15] Clinical trial registration is essential for improving the quality of evidence in physiotherapy research and it is the responsibility of all stake holders (researchers, head of departments and institutions, ethics committees, funding organisations, journal editors, professional associations) to ensure prospective registration of all clinical trials in physiotherapy.

Conclusion

Clinical trial registration is essential to improve transparency and accountability in clinical research. Clinical trial registration is here to stay and it is the responsibility of every researcher and institution to ensure adherence to the required guidelines.

References:

1. National Heart, Lung, and Blood Institute. Why Are Clinical Trials Important? [homepage on the Internet]. No date [cited 2016 Aug 25]. Available from: http://www.nhlbi.nih.gov/studies/clinicaltrials/important
2. Van den Bogert CA, Souverein PC, Brekelmans CT, et al. Occurrence and determinants of selective reporting of clinical drug trials: design of an inception cohort study. BMJ Open. 2015 Jul 7;5(7):e007827. doi: 10.1136/bmjopen-2015-007827.
3. Dwan K, Altman DG, Clarke M, et al. Evidence for the selective reporting of analyses and discrepancies in clinical trials: a systematic review of cohort studies of clinical trials. PLoS Med. 2014 Jun 24;11(6):e1001666. doi: 10.1371/journal.pmed.1001666.
4. Simes RJ. Publication bias: the case for an international registry of clinical trials. J ClinOncol. 1986;4:1529–1541.
5. National Institutes of Health. Clinical Trials.gov: History, Policies, and Laws. [homepage on the Internet]. No date [cited 2016 Aug 25]. Available from: http://clinicaltrials.gov/ct2/about-site/history#NIHReleases.
6. World Health Organization. International Clinical Trials Registry Platform (ICTRP). [homepage on the Internet]. 2016 [cited 2016 Aug 25]. Available from: http://www.who.int/ictrp/en/
7. World Health Organization. International Clinical Trials Registry Platform (ICTRP) WHO Data Set. [homepage on the Internet]. 2016 [cited 2016 Sep 03]. Available from: http://www.who.int/ictrp/network/trds/en/
8. World Health Organization. International Clinical Trials Registry Platform (ICTRP) Primary Registries. [homepage on the Internet]. 2016 [cited 2016 Sep 03]. Available from: http://www.who.int/ictrp/network/primary/en/
9. International Committee of Medical Journal Editors. Clinical Trials Registration.[homepage on the Internet]. 2016 [cited 2016 Sep 03]. Available from: http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/

10. Clinical Trial Registry – India. About CTRI. [homepage on the Internet]. 2016 [cited 2016 Sep 03]. Available from: http://ctri.nic.in/Clinicaltrials/cont1.php#vision

11. Zarin DA, Keselman A. Registering a clinical trial in ClinicalTrials.gov. Chest. 2007 Mar;131:909-12.

12. National Institutes of Health. Clinical Research Policy - Clinical Trials. [homepage on the Internet]. 2016 [cited 2016 Aug 25]. Available from: http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/clinical-research-policy/clinical-trials

13. Hinman RS, Buchbinder R, Craik RL et al. Is This a Clinical Trial? And Should It Be Registered? PhysTher 2015; 95:810-814.

14. Veluswamy SK, Babu AS, Shah P, Maiya AG. Clinical trial registration in physiotherapy research. Perspect Clin Res. 2013;4:191-2.

15. Babu AS, Veluswamy SK, Rao PT, Maiya AG. Clinical trial registration in physical therapy journals: a cross-sectional study. PhysTher. 2014:94:83-90.

***