

Clinical Trial Registry: An essential requirement for physical therapy and health researchers in Pakistan

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Abstract

Clinical trial registry is a free, open access platform which registers clinical trials, often done prospectively, minimizing the risk of selective reporting, publication bias and replication of trials, as well as allowing individuals to participate in the study. A prospective clinical trial registration has been made mandatory by International Committee of Medical Journals Editors (ICMJE), FDA US, World Medical Association (WMA) and International Society of Physical Therapy Journal Editors (ISPJE), followed by a steep increase in the number of registered trials, emphasizing the need and importance of clinical trial registration. Unfortunately, 100% lack of registration of physical therapy articles published recently in Pakistan is due to the unavailability of local registry and laws requiring trial registration. Meanwhile, Pakistani researchers can register their trials at "clinicaltrials.gov" which is a service provided by the U.S. National Institute of Health. Nonetheless, it is very important to create a publicly accessible clinical trial registry and increase awareness regarding clinical trial registration in Pakistan.

Keywords: Clinical trial registry, Research, Publication ethics, Pakistan, History, Physical therapy, Health.

Introduction

World Health Organization (WHO) defines 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".¹ International Committee of Medical Journals Editors (ICMJE) on the other hand defines a clinical trial as, "Any research that allocates participants of any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention and a health outcome".² In June, 2007 however, ICMJE also adopted WHO's definition. An intervention can be a

drug, an invasive procedure such as surgery, any non-invasive procedure such as exercises, behavioural treatment or management, devices or equipment, education or trainings, dietary management or interventions focused at improving quality of life. In short, any research involving any health related intervention to single or multiple groups is a clinical trial.

The objective of this study was to review the trends, development and use of clinical trial registries in Pakistan, especially in the field of physical therapy. Moreover popular registries and studies from different national research journals were scrutinized for the use of clinical trial registration and the findings pertaining to registration are reported. To the best of our knowledge, literature is deficient on this topic. This short communication will provide valuable insights to physical therapists and other health care professionals in Pakistan regarding the importance of clinical trial registration in the field of health care research and its current status in Pakistan.

Search Strategy

An online search was conducted during January-February 2017, using key words such as clinical trial registries, trial registration, interventional study registries and trial databases etc. Boolean words were used to combine search where applicable. Literature search was conducted in two phases. First phase consisted of an online search from electronic search engines and databases including Google Scholar, Pakmedinet, Pubmed, Scopus, Cochrane, PEDro and EBSCO but did not result in substantially relevant literature on the said topic related to Pakistan except for one editorial; however a few international studies related to topic were identified. In the second phase, information regarding the clinical trial registries was collected using similar key words and individual review of guidelines related to trial registration from Google search engine and websites of relevant organizations such as World Health Organization (WHO), International Committee of Medical Journals Editors (ICMJE), World Medical Association (WMA), Committee on publication ethics (COPE) and US National Institute of Health (NIH).

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Clinical Trial Registry

A clinical trial registry is free of cost, open access official platform which involves the registration of a clinical trial. This registration is done before the commencement of the trial; however trials that commenced prior to 2013 can also be registered retrospectively for many journals as shown in Table-1. Clinical trial registration in advance has numerous benefits as it eludes the risk of trials to be

Table-1: Physical Therapy Journals & dates on which they made prospective trial registration mandatory.^{4,20}

Name of the Journal	Date after which prospective trial registration made compulsory
Journal of Physiotherapy	1st January 2013
Physiotherapy	1st January 2013
Physiotherapy Canada	1st January 2013
The Journal of Orthopedic & Sports Physical Therapy	1st January 2013
Journal of Physiotherapy & Sports Medicine	1st January 2014
Brazilian Journal of Physical Therapy	1st January 2014
Norwegian Journal of Physiotherapy	1st January 2014
Manual Therapy	1st January 2014
Physical Therapy & Research	1st January 2014
Journal of Manual and Manipulative Therapy	1st January 2014
Cardiopulmonary Physical Therapy Journal	1st January 2015

replicated needlessly, and also allows the members of the community having specific health issues to recognize the specific trials in which they can take part.³ Most importantly, prior registration also tackles issues like selective reporting and publication bias.⁴

Importance of Clinical Trial Registration

The first ever major registry for health related trials was formed in 1998, followed by registration of numerous clinical trials but most of the clinical trials stayed unregistered till the year 2004.⁴ In 2004, the "International Committee of Medical Journals Editors" (ICMJE) endorsed clinical trial registration and the member journals declared prior clinical trial registration to be compulsory for all clinical trials that were to be conducted after July 1st, 2005.⁵ This was followed by FDA amendment act (FDAAA) of 2007, public law 110-85, title VIII of United states Law requiring investigators to register their clinical trials.⁶ WHO also supported trial registration in a position statement also complimenting Declaration of Helsinki.⁷ In the year 2008, the "World Medical Association" incorporated a new article under the heading of "Research registration and publication and dissemination of results" in the "Declaration of Helsinki" stating that "Every clinical trial must be registered in a publicly accessible registry prior to the recruitment of the first

participant in the study".^{4,8} In 2010 CONSORT guidelines for trial reporting also added trial registration item in guidelines for transparent reporting of trials.⁹ With the passage of time, more and more journals endorsed clinical trial registration, resulting in a rapid increase in registered trials¹⁰ and recently trial registration has been marked as single most valuable way to ascertain unbiased research reporting.¹¹ ICMJE acknowledges all of the primary registries identified by the WHO's "The International Clinical Trials Registry Platform" (ICTRP)² and declared it mandatory for all its member medical journal editors to require from their authors, a prospective registration of the clinical trial in an open access public trial registry before the enrollment of the first participant as a condition for consideration of the manuscript for review.² Hence it is mandatory for the medical journal editors to acknowledge that the listing means implementation of this ICMJE's trial registration policy by the journal, if they wish to request for inclusion of their journal in the ICMJE list of publications on the website. All of this shows the importance of mandatory clinical trial registration for publication of a manuscript. ICMJE enlists 3386 journals of which some recommend addition of clinical trial registration number in manuscript by using phrases and words such as "should," "prefer," "encourage," in instruction to authors for clinical trial registration while others make trial registration requirement mandatory by using "must," "need," or "manuscripts won't be considered". This relaxation by few journals can possibly be due to lack of trial registration in developing countries due to unavailability of publically accessible registries. For such reasons researcher can request to publish the trial without registration number. Such trials can be considered for publication by editor based on level of its content but this exception is rare. It has been recommended to evaluate such papers on case by case basis¹² and provide a supporting statement along with manuscript by researcher to why trial was not registered.^{12,13}

WHO Recognized Clinical Trial Registries

ICTRP was established by the WHO, with the mission of ensuring absolute accessibility of research to everyone involved in health care decision making in order to strengthen the worth and validity of scientific evidence.¹⁴ The WHO's ICTRP is not a clinical trial registry and one cannot register a clinical trial with ICTRP. However ICTRP identifies the primary registries with which one can register his/her research (Table-2).

Clinical Trial Registration in Asia

A steep increase in trial registration was observed on clinicaltrials.gov since ICMJE implemented mandatory

Table-2: Primary registries identified by WHO.¹⁴

Name of Registry	Website
Australian New Zealand Clinical Trials Registry (ANZCTR)	http://www.anzctr.org.au/
Brazilian Clinical Trials Registry (ReBec)	http://www.ensaiosclinicos.gov.br/
Chinese Clinical Trial Registry (ChiCTR)	http://www.chictr.org.cn/
Clinical Research Information Service (CRIS)	http://cris.nih.gov.kr/cris/
Clinical Trials Registry - India (CTRI)	http://ctri.nic.in/
Cuban Public Registry of Clinical Trials(RPCEC)	http://registroclinico.sld.cu/en/
European Union Clinical Trials Register (EU-CTR)	https://www.clinicaltrialsregister.eu/
German Clinical Trials Register (DRKS)	https://drks-neu.uniklinik-freiburg.de/drks_web/
Iranian Registry of Clinical Trials (IRCT)	http://www.irct.ir/
International Standard Randomized Controlled Trial Number (ISRCTN) registry	http://www.isrctn.com/
Japan Primary Registries Network (JPRN)	http://rctportal.niph.go.jp/
University hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN-CTR)	http://www.umin.ac.jp/ctr/
Japan Pharmaceutical Information Center (JAPIC) Clinical Trial Information Center for Clinical Trials, Japan Medical Association	http://www.japic.or.jp/
Thai Clinical Trials Registry (TCTR)	http://www.jmacct.med.or.jp/en/
The Netherlands National Trial Register (NTR)	http://www.clinicaltrials.in.th/
Pan African Clinical Trial Registry (PACTR)	http://www.trialregister.nl/trialreg/index.asp
Sri Lanka Clinical Trials Registry (SLCTR)	http://www.pactr.org/ http://www.slctr.lk/

trial registration in 2005, with a total of a total of 246,843 trials till date, of which 48,299 have been registered from Asia and parts of Middle East. Out of these only 381 trials are from Pakistan, of which 303 are interventional studies and 186 studies have their current status mentioned as completed and 43 studies are currently recruiting or enrolling by invitation.¹⁵ It was observed that between 2007 & 2012 more studies registered for recruitment in Asia than in USA and Europe. South Korea, China, Japan and India showed a marked increase in trial registration but this trial registration substantially increased after local development of policies and measures to implement trial registration. Development of local trial registries in Japan and India also influenced the high number of trials to be registered, which emphasizes the need of National trial registry in Pakistan as well.⁹

Clinical Trial Registry in Pakistan

In Pakistan, promotion of clinical trial registration has been advocated for almost a decade now. An editorial published in 2012 emphasized the importance and need to establish a clinical trial registry.¹⁶ In 2014, in concluding session of 2nd National conference of Pakistan association of medical editors it was recommended to follow the Committee on Publication Ethics (COPE) guidelines tackling issues associated with publication ethics.¹⁷ One of which clearly advocates transparency and recommends the inclusion of clinical trial registry number in published articles,¹³ yet there is still no public trial registry in Pakistan. This presents a significant problem and has been identified as a major reason for lack of

registration of clinical trials along with absence of national legislation and mandatory requirement of registration by ethics committees and funding agencies.⁹

Clinical Trial Registration and Physical Therapy Journals

Even though the journals encouraged clinical trial registration, only 6% of all the physical therapy related clinical trials published in 2009 were registered prospectively.^{18,19} In 2013 it was determined that only 30% of physical therapy trials are registered in publically accessible registry which was still considerably low.⁹ Keeping this in view a joint editorial was published by some of the most prestigious journals of physical therapy; also members of "International Society of Physical therapy Journal Editors" (ISPJE), which emphasized on promotion and implementation of prospective trial registration in physical therapy.^{4,20} After 2013, numerous physical therapy journals have made it mandatory to prospectively register clinical trial before its commencement as shown by (Table-1).⁴ Most of the physical therapy journals however, allow retrospective clinical trial registration for studies conducted prior to 2013.^{4,20} To adhere to and enhance research reporting guidelines such as CONSORT in physical therapy, rehabilitation and disability related researches, in 2014: 28 major disability and rehabilitation journals formed a group to implement these guidelines not only in their journal but also in their field.²¹ This also supports trial registration as it is mandatory requirement to provide trial registration number along with the manuscript in guidelines such as CONSORT.

Trial Registration of Physical Therapy Articles in Pakistan

Since commencement of undergraduate "Doctor of Physical Therapy" (DPT) and postgraduate "Masters in Physical Therapy" (MS-PT) degrees, the numbers of research publications in field of physical therapy have grown tremendously. One of the reasons for this can be that both are research-based degrees requiring students to complete a thesis or dissertation project. Some students conduct Clinical trials in their DPT degree, whereas almost all students enrolled in MS programme of various universities conduct some form of clinical trial. None of these studies are registered in any publically accessible register; reason for being is absence of a national public clinical trial registry. This result in students being unable to get their manuscripts published in international journals particularly of high quality. Currently, there are four physical therapy journals in Pakistan namely the Journal of Physiotherapy and Sports Medicine (JOPSM),²² International journal of Rehabilitation Sciences (IJRS),²³ Journal of Riphah College of Rehabilitation Sciences (JRCRS)²⁴ and Pakistan Journal of Rehabilitation.²⁵ No clinical trials were published in IJRS in 2016, whereas no issues were available for JOPSM and Pakistan Journal of Rehabilitation in online archives for the year 2016.^{22,23,25} Three clinical trials were published in JRCRS, however none of them had a prior clinical trial registration.²⁴ The 3 leading medical journals of Pakistan, Journal of Pakistan Medical Association (JPMA), Pakistan Journal of Medical Sciences (PJMS) and Journal of College of Physicians and Surgeons Pakistan (JCPSP) ranked in W category by higher education commission (HEC) of Pakistan follow the ICMJE guidelines. JPMA and PJMS have specifically mentioned clinical trial registration as mandatory for randomized controlled trials in their "Instructions for Authors" section, however both of them have not specifically asked for prospective clinical trial registration. The three journals published 6 clinical trials (Supplementary material available if required) in subjects of physical therapy in the year 2016, but none of the clinical trials were registered. Five of these clinical trials were published in PJMS and one was published in JCPSP. Although this trend of 100% lack of registration of physical therapy articles published in 2016 is no different from rest of the world where only 30% physical therapy articles are registered as discussed earlier, unavailability of local registry and laws requiring trial registration can be one of the contributing factors.⁹

How can Pakistani Researchers get their Trials Registered?

Any researcher can register his/her trial in a national

registry free of cost but unfortunately there is no public clinical trial registry in Pakistan. One way for Pakistani researchers to get their clinical trials registered is at "clinicaltrials.gov" which is a service provided by the U.S. National Institutes of Health, and registers trials conducted around the world.

The researcher has to contact the "Protocol Registration and Results System" (PRS) administrator of their respective Institute/University/Hospital and the PRS administrator will register the clinical trial for the researcher in the database. For that, the researcher can check the current list of organizations with a PRS account.²⁶ If the researcher's organization does not possess a PRS account, the researcher can identify an individual who can apply for a PRS organization account on behalf of the organization. One can also apply for a PRS individual account; however that is not recommended for most organizations. Keep that in mind, that clinical trial has to be registered prior to the induction of the first participant in the study.

Conclusion

Clinical trial registration has been implemented as mandatory requirement for publication and has been advocated by numerous societies, organization and health care journals worldwide. Yet, trial registration in Pakistan is low, one reason being absence of national clinical trial registry. This leaves room for reporting bias and numerous other research misconducts by researchers, raising a question on quality of research being produced. Development of national clinical trial registry is need of the hour for quality and progress of clinical trials conducted in Pakistan.

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