

An overview of primary registries of WHO's international clinical trial registry platform

Atul Juneja, Jyotsna Gupta¹, Neha Yadav¹, Saurabh Sharma, Yashmin Panchal¹, Tulsi Adhikari, M. Vishnu Vardhana Rao

ICMR-National Institute of Medical Statistics, ¹Clinical Trials Registry-India, ICMR-National Institute of Medical Statistics, New Delhi, India

Abstract

Introduction: WHO's International Clinical Trials Registry Platform (ICTRP) has 17 primary registries that collect the information on the minimum set of items of trial information that appear in the register and these registries are also endorsed by the International Committee of Medical Journal Editors. **Objective:** The objective of this study is to describe the profile of all the primary registries including Clinical Trial Registry-India (CTRI), through features such as magnitude, domain of registration, flagging, audit trail, language, mandatory requirements, and result disclosure. **Methodology:** The profiling of all registries was based on countries and zones, year of establishment, registrant, flagging, conflict of interest, language, documents, result disclosure, type of study, mode of registration, mandate of registration, quality check method, individual patient data statement and translation of content facility. The mode of search used was online which included advanced search, basic search and also from the audio/video manual on their website. **Results:** There are 17 primary registries of ICTRP, the first one International Standard Randomised Controlled Trial Number (ISRCTN) of England being initiated in year 2000 and the most recent being Lebanese registry, in September 2019. The trials registered with these registries range from 301 in Cuba to 53972 in European union's EU Clinical Trials Register. The primary registries in WHO registry network are diverse in functionalities and practices. The characteristics of online registers vary in content and features and to achieve coordinated level of data quality, across all the different registries and to keep a balance in standards of the data collected and validation of that data, the registries are adhering to the minimum data set items laid down by ICTRP. **Conclusion:** The very process of registering the clinical studies helps in promoting the research methods and also raising the standards of research, especially among young researchers. It also helps in reducing the duplicity of research.

Keywords: Clinical Trial Registry-India, Helsinki Declaration, International Committee of Medical Journal Editors, International Clinical Trials Registry Platform, Primary Registries

Introduction

Clinical trial is a research that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.^[1] According to the recommendations of the declaration of Helsinki: "Every clinical trial must be registered in a public accessible database before recruitment of first subject."^[2] In the Ministerial Summit on Health Research that took place in Mexico City, Mexico, in November 2004, participants called for the WHO to facilitate the establishment of "a network of international clinical trials registers to ensure a single point of access and the unambiguous identification of trials," following which, in the year 2005, the WHO-International Clinical Trials Registry Platform (ICTRP) was established with a mission to ensure the complete view of research for all those involved in health care decision-making,

improving research transparency, strengthen the validity and value of the scientific evidence base.^[3]

ICTRP assembles trial data from different clinical trial primary registries and functions as a database from which all the information regarding clinical trials can be accessed globally. ICTRP ensures research transparency by making sure that the complete information of any clinical research is readily available for all agencies involved in health care

Address for correspondence: Dr. Tulsi Adhikari,
Scientist 'E', ICMR-National Institute of Medical
Statistics, Ansari Nagar, New Delhi - 110029, India.
E-mail: tulsi_adhikari2003@yahoo.co.in

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Juneja A, Gupta J, Yadav N, Sharma S, Panchal Y, Adhikari T, *et al.* An overview of primary registries of WHO's international clinical trial registry platform. AYU 2019;40:141-6.

Submitted: 04-Jan-2020

Revised: 05-Mar-2020

Accepted: 05-May-2020

Published: 08-Aug-2020

Access this article online

Quick Response Code:



Website:
www.ayujournal.org

DOI:
10.4103/ayu.AYU_62_20

decision-making, while reinforcing the scientific evidence base for all the clinical researches. At the same time, International Committee of Medical Journal Editors (ICMJE) also mandated the registration of clinical trial in a public trial registry before the first patient enrolment, in order to consider the trial for publication.^[4] The transparent nature of clinical trial registration serves the purpose of prevention of selective reporting of trial outcomes. It also brings in light the types of research and researcher who is conducting the research, which enhances the accountability on a public platform. This also gives an insight into the regulatory scenario of the country where the research is being conducted.

The ICTRP, consisting of primary registries and partner registries, is a globally available one-stop search portal for clinical trials being conducted in the countries of its data providers. Primary registry is a clinical trial registry which meets the specified criteria for content, quality and validity, accessibility, identification, technical capacity and administration in line with WHO-ICTRP registry Network. A primary clinical trial registry must have provisions for collecting information on the minimum items of trial information that must appear in a register, for a trial to be considered fully registered. This is known as the Trial Registration Data Set (TRDS). In addition, a primary registry must also fulfil other criteria set by the WHO. Primary registries are also endorsed by the International Committee of Medical Journal Editors (ICMJE). Currently, there are 17 primary registries that regularly provide data to ICTRP with information on the clinical trials registered with the registry.

The US registry, Clinicaltrials.gov, although a partner registry of the WHO-ICTRP, but it is not a primary registry that shares its trial data with the ICTRP. As per the available literature, few studies have been published which compare different characteristics of clinical trial registries such as industry sponsored versus nonindustry sponsored trials in different countries, causes of globalization of cancer-related clinical trials etc.^[5,6]

The objective of this article is to describe the profile of all the primary registries including Clinical Trial Registry-India (CTRI) and assess the individual features such as language, flagging, type of study as well as the accessibility and robustness of the TRDS for capturing the information about trials from the alternate system of medicine.

Methodology

Data extraction

As per the latest update accessed on September 2019, there are 17 primary registries; the newest addition in the list is the Lebanese registry in the year. The other primary registries, namely Australian New Zealand Clinical Trials Registry (ANZCTR), Brazilian Clinical Trials Registry (ReBec), Chinese Clinical Trial Registry (ChiCTR), Clinical Research Information Service (CRiS), Republic of Korea, Clinical Trial Registry India (CTRI), Cuban Public

Registry of Clinical Trials (RPCEC), EU Clinical Trials Register (EU-CTR), German Clinical Trials Register (DRKS), Iranian Registry of Clinical Trials (IRCT), International Standard Randomised Controlled Trial Number (ISRCTN), UK; Japan Primary Registries Network (JPRN), Thai Clinical Trials Registry (TCTR), The Netherlands National Trial Register (NTR), Pan African Clinical Trial Registry (PACTR), Peruvian Clinical Trial Registry (REPEC) and Sri Lanka Clinical Trials Registry (SLCTR) were accessed through ICTRP website that hyperlinks the websites of all primary registries.

Some registries provide their data in the native language of the country, which was translated using the translation service provided on their website.

The mode of search used was online which included advanced search, basic search and also from the audio/video manual on their website to understand the standard operating procedures of the individual registry, last accessed on July 3, 2019.

The profiling of all registries was based on countries and zones, year of establishment, registrant, flagging, conflict of interest, language, documents, result disclosure, type of study, mode of registration, mandate of registration, quality check method, individual patient data statement, and translation of content facility. The search also included about the studies on traditional/alternate system of medicines through ICTRP platform using keywords "Traditional Medicine, Ayurveda, Unani, Siddha, Homeopathy and China Medicine."

Guiding principles of the primary registries of WHO

The basic attributes of all clinical trials registries include a website [Table 1], homepage, contact and search facility for guidance. There are other features in the individual registries that may differentiate the primary registries, without compromising on the mandate set for data capture by ICTRP.

Countries and zone

Primary registries usually register studies originating under the jurisdiction of their own country as well as for the countries which do not have a primary registry of their own except for the registries of European Union, Africa and Netherlands. Australia and New Zealand are the only countries which share a common registry. The National Institute of Public Health in Japan integrates data from all three registries of the country, namely, University Hospital Medical Information Network, Japan Pharmaceutical Information Centre and Japan Medical Association Center for Clinical Trials.

Primary registries are categorized in five zones, namely Europe, Australia, Asia, Africa and Latin America.

Year of establishment

Among the primary registries, ISRCTN was the first to be launched as the primary registry of WHO in the year 2000 followed by Europe, China, Sri Lanka and India.

As on July 3, 2019, EUCTR established in the year 2004 had registered highest number of studies (53972) followed by 41,143 by Japanese registry, 24,088 by Chinese registry and

20,017 by Indian registry. The number of registered clinical studies for various registries is shown in Table 2.

Responsibility of registration and final registration

A registrant is an authority figure, responsible for registering a clinical trial, in a primary registry. Among all, registries responsibility and authentication of all datasets lies with the registrant, principal investigator, sponsor, except for Peru and Brazil where a legal representative is given the responsibility of uploading and updating the information for trial registration.

Flagging

According to ICTRP, flagging is defined as publishing a message or symbol, to indicate a category to which

the registration of study belongs, i.e., prospectively or retrospectively. With strong recommendation from the ICTRP, World Medical Association and ICMJE, certain registries, including India now accepts only prospective registration, i.e., they do not register studies that have begun enrolling patients, however, countries such as United Kingdom, China, Republic of Korea, Thailand and Peru continue to register retrospective studies also.

Audit trail

The primary registries of WHO have some individual characteristics which may vary sometimes among different countries but definitely not compromising on the standard

Table 1: Categorization of primary registries as per zone

Zone	Country	Name of registry	Website link
Europe	European Union	EU-CTR	https://www.clinicaltrialsregister.eu
	Germany	DRKS	https://www.drks.de/drks_web
	Netherlands	The NTR	https://www.trialregister.nl
	United Kingdom	ISRCTN	http://www.isrctn.com
Australia	Australia and New Zealand	ANZCTR	http://www.anzctr.org.au
Asia	China	ChiCTR	http://www.chictr.org.cn/index.aspx
	Japan	JPRN	https://rctportal.niph.go.jp/en
	Republic of Korea	CRiS	http://cris.nih.go.kr/cris/en/use_guide/cris_introduce.jsp
	Thailand	TCTR	http://www.clinicaltrials.in.th
	India	CTRI	http://ctri.nic.in/Clinicaltrials/login.php
	Sri Lanka	SLCTR	http://www.slctr.lk
	Iran	IRCT	http://www.irct.ir
Africa	Pan Africa	PACTR	https://pactr.samrc.ac.za
Latin America	Brazil	ReBec	http://www.ensaioclinicos.gov.br
	Cuba	RPCEC	http://registroclinico.sld.cu/en/home
	Peru	REPEC	https://ensayosclinicos-repec.ins.gob.pe/en

EU-CTR: European clinical trials register, DRKS: German Clinical Trials Register, NTR: Netherlands National Trial Register, ISRCTN: International Standard Randomised Controlled Trial Number, ANZCTR: Australian New Zealand Clinical Trials Registry, ChiCTR: Chinese Clinical Trial Register, JPRN: Japan Primary Registries Network, CRiS: Clinical Research Information Service, TCTR: Thai Clinical Trials Register, CTRI: Clinical Trials Registry - India, SLCTR: Sri Lanka Clinical Trials Registry, IRCT: Iranian Registry of Clinical Trials, PACTR: Pan African Clinical Trial Registry, ReBec: Brazilian Clinical Trials Registry, RPCEC: Cuban Public Registry of Clinical Trials, REPEC: The Peruvian Clinical Trials Registry

Table 2: Establishment of primary registries in chronological order and total number of registrations

Primary registry	Year of establishment	Total number of registered trials (As on date July 3, 2019)
England (ISRCTN)	2000	18327
European Union (EU-CTR)	2004	53972
Iran (IRCT)		21127
China (ChiCTR)	2005	24088
Sri Lanka (SLCTR)	2006	316
India (CTRI)	2007	20017
Australia and New Zealand (ANZCTR)		17806
Africa (PACTR)		1667
Cuba (RPCEC)		301
Peru (REPEC)		1812
Brazil (ReBec)	2008	3050
Germany (DRKS)		8397
Japan (JPRN)		41143
Thailand (TCTR)	2009	3037
Netherlands and Dutch (NTR)		7840
Republic of Korea (CRiS)	2010	4099

guidelines laid down by ICTRP of which one of the most important is that the trials from none of the registries can be removed once registered. Most of the registries have provision for displaying the audit trail which means that any change made by the registrant to the trial dataset will be recorded in the registry and will be visible in the public domain. Cuban registry (RPCEC) and German Registry DRKS) do not have such provision.

Data transfer to WHO ICTRP

All primary registries periodically transfer details to the ICTRP. The registration data set of all the primary registries has the provision for recording the details if the trial is registered in any other registry as the secondary identity. The Korean clinical trial registry does not transfer the details of the trials to ICTRP if it has a secondary identification, to avoid the duplicity in ICTRP search portal, whereas other registries transfer the data set on the regular basis irrespective of having secondary identification. The German registry fetches the data if the trial is registered elsewhere through its data management mechanism.

All registries agree, as part of the registration process, to search the WHO Search Portal to ascertain if the trial has already been registered on another WHO Primary Registry.^[1] Most of the registries are recording the information on disease condition in text but switching over to standardized taxonomy is very important. Data capture in terms of disease condition based on the International classification of disease is being observed by India (CTRI) and Iran ISRCTN (information is available through individual websites). As the purpose of having a primary registry is to make the clinical research completely transparent this would further strengthen the mandate of no profit, hence in majority of the registries, the trials can be registered free of cost, except Sri Lanka (SLCTR) and Iran (ISRCTN).

Language

A common barrier in sharing scientific knowledge and information is the language. English is considered to be a universally accepted language. All registries are functioning in English, although there are a set of registries that also use a second or third language for this purpose. Chinese can be used in ChiCTR; Dutch in NTR, European Union official languages in EU-CTR, German in DRKS, Persian in IRCT, Portuguese and Spanish in ReBec, Japanese in JPRN; Korean in CRiS, while Spanish is used as a second language in both RPCEC and REPEC.

Requirement of documents for registration

Ethics Committee Approval is a mandatory document to register a clinical trial in ISRCTN, ANZCTR, PACTR, REPEC, DRKS, JPRN, SLCTR, TCTR and CRiS registries. CTRI requires EC approval as well as regulatory approval (Drug Controller General of India), wherever applicable. IRCT and ReBec both require EC approval and protocol to register a trial. ChiCTR asks for EC approval, protocol and informed consent form for registering clinical trials.

Result Discloser

ISRCTN, EU-CTR, ChiCTR, ANZCTR, PACTR, REPEC, DRKS, JPRN and CRiS make it mandatory for the results of a registered clinical trial to be disclosed; ReBec puts no such obligation for the clinical trials registered. CTRI is in the process of developing a standardized platform for reporting of result disclosure for all the clinical trials. At present, there is a provision to put brief results in the open text. It was not possible to ascertain through website, if it was mandatory or not to disclose the results for RPCEC, SLCTR, TCTR, NTR and IRCT.

Type of studies

Registering an interventional trial is mandatory in all the registries. Almost all Asian registries register both interventional and observational studies. It enables the academic research under the ambit of ethical practice in the clinical research and raise the standards of postgraduate research in the country. The registry of European Union only registers the medicinal interventional study and Germany promotes the registration of prognostic studies separately.

Mode of registration

Most of the primary registries only allow clinical trial registration to be done online, except, CRiS which allow the use of online/mobile web and PACTR permit registration through online/Email/Post/Fax. A good development has been made by the Korean registry to have a mobile application, with the intention to facilitate researcher and patient anywhere, even in a clinic.

Quality check

As already mentioned that the responsibility and authentication of all datasets lies with the registrant, however, data are validated both manually as well as electronically and sent back to the registrants for modifications by majority registries. Japan is the only country that registers information without any manual/electronic audit of details; ANZCTR allows quality check to be done only electronically through E-mail.

Trials from traditional/alternate system of medicine

The clinical studies from the traditional system of medicine are registered in these primary registries. The major contribution is from China (ChiCTR) and India (CTRI) followed by Iran (IRCT). A number of trials are also registered on Clinical Trials. gov. Although, Clinical Trials. gov is not a primary registry of ICTRP, but contributes to the global pool of data.

It may be mentioned that the information on such studies is being captured using the same set of TRDS, which is used for the registration of trials from the modern system of medicine.

Translation facility

Registries such as ReBec, REPEC, RPCEC, JPRN, ChiCTR and DRKS allow the option of translation on their websites, as they have other primary language of input.

Discussion

The primary registries in WHO registry network are diverse in functionalities and practices. The registries usually function as per the guidelines provided by the laws of their respective countries and are under the control of ministry of health or equivalent authority. The characteristics of online registers vary in content and characteristic features. In order to achieve coordinated level of data quality across all the different registries and to keep a balance in standards of the data collected and validation of that data, there has to be a minimum standard for execution and resolution followed by these registries.

The registration of all interventional trials is a scientific, ethical and moral responsibility of registrant according to both ICTRP and ICMJE. Food and Drug Administration Amendments Acts of 2007 also does not make the registration of observational studies mandatory.

However, some of the registries including the CTRI undertake the registration of both interventional trial as well as observational studies. This policy is in line with the WHO dictum of 'when in doubt, register'. The purpose and benefit of the database are likely to be served more effectively if a comprehensive account of all types of studies being conducted is available. In order to publish clinical trials in many of the reputed journals, registration of the clinical trial is mandatory, but not all clinical trials are conducted with the goal of publication.^[7]

National legislation, of the countries with primary registry, is pivotal in the implementation of registration for all clinical trials.^[8] Any legislation and laws in place always assist in curbing malpractices at all levels.

According to WHO-ICTRP, every registry needs to maintain the data about every clinical trial, on its registry network in English language. However, it is found that some registries allow the use of native language for submission of clinical trials, e.g., many of the studies in JPRN were written entirely in Japanese, which could even have impacted the information extracted by us. Taking in consideration, that not all registry staff may be equally capable in English, registries are allowed to translate these standards in the native language. In such cases, the responsibility for any translation is upon the individual registries. ICTRP insists that a minimum of two qualified people confirm the accuracy of such translations.^[9]

For investigators/clinician/health personnel, the database should provide information on the type of research and the results of the trial after it is completed so that the relevant information regarding the drug or intervention can be made public and the risk benefit ratio can also be assessed keeping in mind the rights of the developer. In this era of evidence-based medicine, mandatory result disclosure will further strengthen the evidence and reduce publication bias. Dissemination by respective registries needs to be done on a larger scale including both research organizations as well as medical

institutions, to further improve the content and functioning of these registries and also making them more user friendly.

Registry is expected to be a tool that will drive the future, health-care information for researchers, patients and public one in all for better healthcare outcomes and this can be well utilized when search as a tool is user friendly and information is easily accessible. The search facility should enable the user to filter results utilizing various combinations such as disease condition, location, drug name, age, gender etc., if needed. If the user is searching for information which is not available, then they could label it for any new alert of additional information which can be notified to the concerned registry to further improve. User feedback from the registrant can also be made an integral part, once the study gets registered. Second, the information also needs to be comprehensive and easily understood by the lay public. There should be customized searches for both the general public and clinicians/researchers for further increasing the utilization of the registries.

While it is mandatory for all registries, to register clinical trials prospectively, i.e., before the enrolment of the first patient (in accordance with the declaration of Helsinki and guidelines of ICMJE, REF number may be given instead), some primary registries do undertake retrospective registration as well. However, complete accessibility, accountability and transparency can only be achieved when the trial is registered prospectively.

The ethical and scientific importance of result disclosure is very well recognized as this will help in the reduction of publication bias in clinical trials research as well as encourages trial sponsor(s) to follow through on policies and quality assurance processes to improve the quality of published records. Implementation of existing laws and disclosure of result summaries on registries massively reduces the publication bias in the clinical development. This will assist in attaining the ultimate motive of setting of the primary registries.^[10]

A study by Zhang *et al.*^[11] states the requirement for customized data set items for studies from the traditional systems of medicine as an extension version of WHO TRDS. The customized set of TRDS data set items should include several special requirements for studies from different types of the traditional system of medicines.

Conclusion

In order to achieve increased transparency on clinical trial conduct and reporting, better synchronization of data, decrease in publication bias and improvement in information available to general public as well as people associated with clinical trials such as patients, healthcare providers, ethics committee, regulatory authority and researcher, it is vital that the registration of clinical trials is made mandatory by the national legislation of respective primary registries. It is also felt that prospective registration is made compulsory by all primary registries and remains as the only mode of

registration available to a registrant. Results disclosure of registered clinical trials should become obligatory to improve transparency. Failed outcomes and termination of trials with the reason of failure will give credibility to the information without a bias. An evaluation of data and assessment of functionality, strength and weakness, is needed to be conducted so as to make it more robust.

The very process of registering the clinical studies helps in promoting the research methods and also raising the standards of research, especially among young researchers. It also helps in reducing the duplicity of research. Although challenges still remain, the comprehended waste information provides the opportunity to explore the data for health planning through in-depth analysis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Available from: <https://www.who.int/ictip/en/>. [Last accessed on 2019 Jul 03].
2. Available from: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>. [Last accessed on 2019 Jul 03].
3. Available from: https://apps.who.int/iris/bitstream/handle/10665/20304/A58_22-en.pdf?sequence=1&isAllowed=y. [Last accessed on 2019 Jul 03].
4. Available from: http://www.icmje.org/news-and-editorials/clinical_trial_reg_jun2007.html. [Last accessed on 2019 Jul 03].
5. Atal I, Trinquart L, Porcher R, Ravaud P. Differential globalization of industry- and non-industry-sponsored clinical trials. *PLoS One* 2015;10:E0145122.
6. Barrios, CH, Werutsky G, Martinez-Mesa J. The global conduct of cancer clinical trials: Challenges and opportunities. *Am Soc Clin Oncol Educ Book* 2015: 35, e132-139. [Doi. org/10.14694/EdBook_AM.2015.35.e132].
7. Pinto RZ, Elkins MR, Moseley AM, Sherrington C, Herbert RD, Maher CG, *et al.* Many randomized trials of physical therapy interventions are not adequately registered: A survey of 200 published trials. *Phys Ther* 2013;93:299-309.
8. Bian ZX, Wu TX. Legislation for trial registration and data transparency. *Trials* 2010;11:64.
9. Fujii H, Yukawa K, Sato H. International comparison of data from International Clinical Trials Registry Platform-Registered Clinical Trials. *Health* 2016;8:1759-65.
10. Deane BR, Porkess S. Clinical trial transparency update: An assessment of the disclosure of results of company-sponsored trials associated with new medicines approved in Europe in 2014. *Curr Med Res Opin* 2018;34:1239-43.
11. Zhang X, Tian R, Yang Z, Zhao C, Yao L, Lau C, *et al.* Quality assessment of clinical trial registration with traditional Chinese medicine in WHO registries. *BMJ Open* 2019;9:e025218.