Review Article

CTRI – Clicking to greater transparency and accountability

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Abstract

A clinical trial registry (CTR) is an official platform for registering a clinical trial (CT) with an objective of providing increased transparency and access to CTs to the public at large. Clinical Trials Registry - India (CTRI) is a free online public record system for registration of CTs being conducted in India. The vision of the CTRI is to ensure that every CT conducted in the region is prospectively registered with full disclosure of the trial data set items. With more number of CTs being conducted in the country, with a large number being global multicentre trials, it is binding on the industry/investigators/sponsor to comply with the requirements laid down. While there are pros and cons, there is enough scope for improvement of CTRI.

Key words: Clinical trial registry, clinical trials registry-India, compliance, regulatory

CLINICAL TRIAL REGISTRY – AN INTERNATIONAL PERSPECTIVE

The United States (US) was one of the first countries to start off with CTR when the ClinicalTrials.gov was established by Section 113 of the Food and Drug Administration Modernization Act of 1997 (FDAMA 113). It was launched by the National Institutes of Health in February 2000 (http://clinicaltrials.gov/). The European Union (EU) CT database, EudraCT was set up on 1st May 2004. The EU CTR website (https://www.clinicaltrialsregister.eu) was however, launched later by the European Medicine Agency (EMA) on 22nd March 2011. In September 2004, the International Committee of Medical Journal Editors (ICJME) issued a statement regarding CT registration.[1] The ICMJE announced a new policy to reduce potential misrepresentation of CT results in publications. As per the ICMJE policy it required mandatory registration of CTs before enrollment of the first patient as a precondition for consideration for publication. Further, the statement also specifies particular data that must be provided by the sponsor to an acceptable registry.[2] Globally, a strong need was felt to make CT information more widely available with the registration process being standardized. In 2005, World Health Organization (WHO) took the lead to establish the International CTR platform (ICTRP), a one stop search portal (http://www.who.int/ictrp/ en/) for identification of trials fed from existing CTRs that meet standard criteria for the exchange of essential trial data (20 key item details) before enrollment of the first patient. Apart from US and EU, the other countries which have CTR include Africa (http://www.pactr.org/) Australia (http://www.anzctr.org.au), Brazil (http://www.ensaiosclinicos.gov.br), Canada, China (http://www.chictr.org), Cuba (http://registroclinico.sld.cu), Germany (http://www.drks.de), India (http://www.ctri.nic.in), Iran (http://www.irct.ir), Japan (http://umin.ac.jp), South Africa (http://www.sanctr.gov.za/), South Korea (http://ncrc.cdc.go.kr/cris/index.jsp), Sri Lanka (http://www.slctr.lk/), Netherlands (http://www.trialregister.nl/trialreg/index.asp), New Zealand (http://www.anzctr.org.au) etc. The primary registers are WHO -selected ones which are managed by not-for-profit entities who accept registrations for any interventional trials, delete duplicate entries from their own register, and provide data directly to the

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WHO.[3] Another search portal is the IFPMA CT portal (http://clinicaltrials.ifpma.org), which has been initiated by the pharmaceutical industry for providing convenient "one-stop-shop" for published CT information.

CLINICAL TRIALS REGISTRY - INDIA

CTRI is not for profit organization and is hosted at the Indian Council of Medical Research's (ICMR's) National Institute of Medical Statistics (NIMS). CTRI was established in October 2005 and was officially launched on 20th July 2007 however, at that point in time registration was on a voluntary basis. Since 15th June 2009, CT registration in the CTRI has been made mandatory before enrollment of the first subject by the Drugs Controller General (India) (DCGI).The CTRI adopts the WHO definition of a CT: '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.'[4,5] However, many academic researchers and investigator initiated studies are still being done with new drugs without taking approval from DCGI which is against the Drugs and Cosmetics Rules. The DCGI has issued the notice on 16th Aug 2012, making it clear to all concerned that no CT for a new drug, whether for clinical investigation or any clinical experiment by any institution, shall be conducted except under and in accordance with the written permission of the licensing authority.[6] In the proposed draft rule 122 DAC, dated 18th Nov 2011 from the Ministry of Health and Family Welfare (MHFW) which may be called the Drugs and Cosmetics (3rd Amendment) Rules, 2012 – the clause (1)(d) states "CT shall be registered at CTRI before enrolling the first patient in the study". This will formally bring the process of registration under the legislation. In this review, the author has attempted to introspect and jot down the advantages and shortcomings of CTRI in the Indian context and suggested possible areas of improvement for this registry taking cue from other such registries available globally.

POSITIVE FEATURES OF CLINICAL TRIALS REGISTRY - INDIA

- Registration is free of charge to anybody with internet access thereby encouraging the sponsors or their designated surrogates (collectively known as data provider/applicant) to register their trials.
- Clarifications/confirmatory mails are sought by sending mails to applicant/investigators/contact persons prior to registration.
- Once registered, all updates and changes get recorded and viewable in the public domain.
- As CTRI has additional items/fields over and above the 20 items in the WHO-ICTRP trial registration data sets (like phase of trial, study sites, names of ethics committees (ECs) and approval status, method of generating randomization sequence, blinding/masking, estimated trial duration, brief summary etc) it would influence and strengthen the study design, conduct and eventual reporting of CTs.
- Once registered in the CTRI, the WHO trial registration data sets are transferred to the central repository of the WHO's ICTRP search portal which would give the trials greater visibility.
- The trial results will qualify to be considered for publication in journals that endorse the ICMJE position on prospective trials registration.
- Helps in providing a base template for designing the study protocol and also leaves scope for raising the standard of study design/trial.
- Helps to expedite the overall study duration as there is a ready database of trials done in a similar setting/indication/investigators which can be capitalized upon.
- Patients can surf to identify CTs they may wish to participate in.
- Helps in informed healthcare decision-making for healthcare providers, policy- makers and funding agencies.
- ECs can use it to evaluate a particular trial and see the status of regulatory and other site EC approvals.
- Journal editors and systematic reviewers can use to determine adherence to the study protocol including amendments, verify the outcome measures etc., using this database.
- It can be used as a good market intelligence tool by companies to identify what their competitors are up to; what stage of development they are in and what are the drugs being tried for a particular indication.
- CTRI is open in accepting registration of CTs not just conducted in India, but those conducted in other countries in the region, which do not have a primary register of its own.

LIMITATIONS OF CLINICAL TRIALS REGISTRY - INDIA

- Although any researcher who plans to conduct a trial involving human subjects with any intervention (drugs, device, surgical procedure etc.) is expected to register the trial at CTRI, the CTRI cannot ensure that all trials will be registered.[7] Many investigator driven trials still go unregistered.
- As part of quality control (QC) checks, the CTRI does not cross verify against "all" the elements entered. For example, thorough compliance checks are not performed for the "study protocol" *per se* to verify if the "applicant" is providing the correct/abridged/complete information.

- Once a CT is registered, the "data providers" are expected to regularly update the trial status or other aspects as the case may be throughout the lifecycle of the CT by requesting CTRI to unlock the database. However, this does not happen in many cases.
- There are no hyper-linking to relevant documents/ information in other online biomedical resources like PubMed/MedlinePlus etc. to access related health topics.
- Detailed search filters supporting multiple selection options are not there for instance search by year of CT approval, age of the subject, gender etc.
- Under certain data fields, CTRI does not accept symbols which sometimes becomes challenging for the "data providers" to enter with the correct representation.
- 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, a temporary UTRN is being automatically generated and assigned by the CTRI software application to any trial that is being processed for submission.[8]

SCOPE FOR IMPROVEMENT

- To encourage compliance, system generated reminder mails could be sent to the applicant. Defaulters who do not periodically update the trail status should be listed on the website.
- Registration if done through unique "organizational accounts" will help in minimizing chances of duplicate registration numbers being created for the same trail, and would help ensure better quality control.[9]
- CTRI staff can work actively with DCGI staff and access the registered trials to conduct self compliance checks.
- Registration of post marketing surveillance and bioavailability/bioequivalence (BA/BE) studies is currently not mandatory in CTRI though there is drug intervention involved. Though there is bound to be resistance from the industry, enforcing it at least for "new drugs" (e.g., new strength) will serve scientific and ethical function apart from regulatory compliance.
- Minor editorial issues (e.g., typos, spelling errors, controlled vocabulary) in the items being fed, can be corrected during QC checks by having some IT enabled search engine tools [such as G-spell; SPECIALIST Lexicon; Medical Subjects Heading (MeSH) vocabulary] as used by ClinicalTrials.gov.[2]
- CTRI can take feedback from different user groups and attempt at modifying the site as necessary to adapt to the changing regulatory requirements.
- Web content can possibly be expanded beyond English to other languages (like Hindi) to have a wider reach.
- Currently there is no data element for "study results" in CTRI. Due to vested interests, negative trial results are usually not brought to the general public/physicians notice. Inclusion of the same as part of CTRI update will help in improving research transparency and would strengthen the validity and value of the scientific evidence base. In fact the ICMJE has recommended quite some time back a standard abstract format for reporting of CT results.[10] EU also has future plans to include publication of summaries of CT results with the launch of Eudra CT V 9.0.
- System generated e-mail alerts can be sent to users every time a CT of their interest is registered, provided one subscribes to it.

CONCLUSIONS

With advocacy and dissemination of the need for CTR, the number of trials registered on CTRI has phenomenally grown over a period of time, which reflects greater transparency, accountability at the same time safeguarding patient's interest. Some of the points listed above could be viewed as advantageous for some while being disadvantageous for others. Additional funding from ICMR, the Department of Science and Technology (DST) and the WHO could help in raising the current standards and minimize the shortcomings.

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