Original Article

Has mandatory prospective registration of all studies brought about a change? A 1-year audit of studies registered in the Clinical Trials Registry of India [CTRI] before and after April 1, 2018

Nayana S. Shetty, Rachana A. Salvi, Urmila M. Thatte[1], Nithya J. Gogtay[1]

Departments of Pharmacology and Therapeutics and [1]Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India

Abstract

Introduction: The Clinical Trials Registry of India (CTRI) that initially permitted retrospective registration moved to mandatory prospective registration of studies with effect from April 1, 2018. The present study was an audit that compared registration 1 year post the rule versus a year prior to it.

Materials and Methods: All studies registered with the CTRI from April 1, 2017, to March 31, 2018, and subsequently from April 1, 2018, to March 31, 2019, were included for the analysis. The extents of retrospective registration a year pre and a year post April 1, 2018, of all studies were evaluated.

Results: A total of 4628 studies were registered prior to April 1, 2018, and 5438 post that. Pre April 1, 2018, 2687 / 4628 (58.06%) studies were retrospectively registered, while post that, 1100 / 5438 (20.23%) studies were retrospectively registered (cOR: 5.46 [5.0, 5.9], $P < 0.001$). Regardless of whether the studies were PG theses, regulatory studies, observational studies, or interventional studies, there was a statistically significant reduction in the number retrospectively registered post April 1, 2018, relative to the year predating it.

Discussion and Conclusion: The success of CTRI's decision to move to prospective registration is seen in the overall reduction in the total number of retrospective registrations from nearly two-thirds in the year predating April 1, 2018, to just a quarter in the year post that, indicating significant inroads made by the CTRI with regard to raising awareness. Some regulatory studies continue to be retrospectively registered and this presents a significant ethical and regulatory breach. This could be potentially addressed by linking ethics committee approval with trial registration.

Keywords: Database, ethics committee, trials

Address for correspondence: Dr. Nithya J. Gogtay, Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai - 400 012, Maharashtra, India.
E-mail: nithyagogtay@kem.edu
Received: 15-04-20, **Revised:** 30-04-20, **Accepted:** 21-05-20, **Published:** 08-01-21.

INTRODUCTION

The Clinical Trials Registry of India (CTRI) was first established in October 2005 and subsequently formally launched on July 20, 2007. It is Asia's first clinical trials registry[1] established with the objective to provide an

Access this article online	
Quick Response Code:	Website: www.picronline.org
	DOI: 10.4103/picr.PICR_89_20

How to cite this article: Shetty NS, Salvi RA, Thatte UM, Gogtay NJ. Has mandatory prospective registration of all studies brought about a change? A 1-year audit of studies registered in the Clinical Trials Registry of India [CTRI] before and after April 1, 2018. Perspect Clin Res 2021;12:72-5.

official platform for India to register its clinical trials, improve transparency, and also provide access to trials to the populace of the country. It was also envisaged as a platform for trials registration for countries that did not have a registry of their own.[2] At the point of its launch, CTRI registration was voluntary. CTRI also permitted retrospective registration of studies in an attempt to encourage researchers to register their trials.

An audit carried out by us earlier that evaluated the nature and extent of retrospective registration with the CTRI (2016) showed that of the 1147 studies registered, 719 (63%) were retrospectively registered. While studies funded by the pharmaceutical industry were four times more likely to be prospectively registered (relative to studies not funded by the pharmaceutical industry), postgraduate theses were twice as likely to be retrospectively registered relative to other studies.[3]

The CTRI received a major fillip on June 15, 2009, when the Drugs Controller India made prospective registration (registration prior to enrolment of the first participant) of all regulatory studies mandatory.[4] In an important move, the CTRI announced that with effect from April 1, 2018, all studies (and not just regulatory studies as had been mandated by the Drug Controller General of India in 2009) had to be prospectively registered.[4] Against this backdrop, we carried out the present study with the primary objective of evaluating the nature of registrations including whether prospective or retrospective, type of study, and type of sponsor subsequent to the implementation of this rule.

MATERIALS AND METHODS

Ethics and selection criteria

The institutional ethics committee accorded a waiver for the study as the data were available in the public domain (EC-OA-83 / 2019). All studies registered with the CTRI 1 year before April 1, 2018, and 1 year after were evaluated.

Search strategy and dates searched

The CTRI (www.ctri.nic.in) was searched for all studies using the following keywords: "CTRI/year/month number" and the dates searched were April 1, 2017, to March 31, 2018, and April 1, 2018, to March 31, 2019.

Outcome measures

These were the total number of studies registered a year before and a year after April 1, 2018, the nature of the studies (postgraduate theses, observational studies, interventional studies, and regulatory studies), and the number in the year pre and post April 1, 2018, that were retrospectively registered. We also evaluated associations between the timing of registration (i.e., in the year before or after April 1, 2018) and the retrospectively registered studies. We also evaluated the association between the timing of registration (i.e., whether study was registered in the year before or after April 1, 2018) with the number of retrospectively registered studies.

Statistical analysis

Both descriptive and inferential statistics were applied to the data. Categorical data such as total number of retrospective (or prospective) registrations were expressed as proportions. Association between the number and nature of studies was initially subjected to the Chi–square test, followed by the calculation of a crude odds ratio (with 95% confidence interval). Data entry was done using Microsoft Excel and all analyses were done at 5% significance using Microsoft Excel and SPSS version 25.0.

RESULTS

Demographics

Overall, a total of 4628 studies were registered during the period April 1, 2017, to March 31, 2018. Subsequently (April 1, 2018, to March 31, 2019), a total of 5438 studies were registered.

Nature of registration: Overall analysis

In the year predating April 1, 2018, 2687 / 4628 (58.06%) studies were retrospectively registered. In the year post April 1, 2018, 1100 / 5438 (20.23%) studies were retrospectively registered, with this difference being statistically significant ($P < 0.001$).

Nature of studies: Overall analysis

(a) PG theses: It was seen that 2584 / 4628 (55.88%) theses were registered in the year predating April 1, 2018, while post that date, 3337 / 5438 (61.36%) theses were registered. (b) Observational and Interventional studies: A total of 1224 / 4628 (26.45%) observational studies were registered pre April 1, 2018, while post that date, 1554 / 5438 (28.58%) studies were registered; similarly, 3404 / 4628 (73.55%) interventional studies were registered prior to April 1, 2018, while in the year post that date 3884 / 5438 (71.42%) were registered. (c) Regulatory studies: A total of 268 / 4628 (5.79%) studies were registered in the year predating April 1, 2018, while 278 / 5438 (5.11%) were registered in the year following April 1, 2018. Barring regulatory studies, there was a statistically significant increase ($P < 0.001$) in number of all other type of studies registered post April 1, 2018 [Table 1].

Analysis of association between retrospectively registered studies and timing of registration (i.e., before April 1, 2018, or after)

Regardless of whether the studies were PG theses, regulatory studies, observational studies, or interventional studies, there was a statistically significant reduction in the number retrospectively registered post April 1, 2018, relative to the year predating it. Furthermore, regardless of the sponsor (pharmaceutical industry, government-funding agency, academic institutions, investigator initiated, miscellaneous funding, and source of funds not mentioned), all the studies showed a statistically significant reduction in retrospective registration post April 1, 2018. The details are given in Table 2.

DISCUSSION

The present study evaluated registration of studies in the CTRI 1 year after April 1, 2018, when the CTRI announced that only prospective registration will be permitted and compared it with registration a year prior to that. We found a statistically significant reduction in retrospective registration regardless of the nature of the study and type of sponsor.

The CTRI initially started off as a database that expected researchers to voluntarily register their studies and a significant impetus to it was given by the Indian regulator who made it mandatory for prospective registration of regulatory studies with effect from June 2009. Its own decision to implement prospective registration from April 1, 2018, likely stems from the fact that researchers and nonregulatory studies continued to be registered retrospectively. This despite the fact that the Declaration of Helsinki (2008 version)[5] clearly recommended prospective registration of studies in a publicly accessible database. The success of CTRI's decision to move to prospective registration is visible in the overall reduction in the total number of retrospective registrations from nearly two-thirds in the year predating April 1, 2018, to just a quarter in the year post that, indicating significant inroads made by the CTRI with regard to raising awareness. This will make the conduct of studies in the country more ethical and research more transparent.

An important finding was a significant reduction in retrospective registration regardless of the nature of studies. We found a crude odds ratio of nearly 6 for the reduction in retrospective registrations of PG theses, observational studies, and interventional studies. What remains moot is why researchers continue to register studies retrospectively. A study by Hunter[6] who analyzed trends of registration in the Australian New Zealand Clinical Trials Registry among 148 respondents showed that the most common reason cited was lack of awareness (56%) and this included

Table 1: Demographics of registered studies

	From April 1, 2017, up to March 31, 2018, n_1 (%)	From April 1, 2018, up to March 31, 2019, n_2 (%)
Total number of studies registered	4628	5438
Nature of registration		
Retrospective registration	2687 (58.06)	1100 (20.23)*
Nature of study		
Postgraduate theses	2584 (55.88)	3337 (61.36)*
Observational studies	1224 (26.45)	1554 (28.58)*
Interventional studies	3404 (73.55)	3884 (71.42)*
Regulatory studies	268 (5.79)	278 (5.11)

*$P<0.001$

Table 2: Association between retrospectively registered studies and timing of registration (i.e., before April 1, 2018, or after)

	Retrospectively registered		Crude OR (95% CI)
	From April 1, 2017, up to March 31, 2018 (n_1=4628)	From April 1, 2018, up to March 31, 2019 (n_2=5438)	
Nature of study			
PG theses	1624 (35.09)	775 (14.1)	5.59 (4.99-6.26)*
Regulatory	32 (0.69)	10 (0.18)	3.55 (1.70-7.38)*
Observational	698 (57.0)	304 (19.56)	5.45 (4.60-6.46)*
Interventional	1989 (58.43)	796 (20.49)	5.45 (4.91-6.04)*
Source of funding			
Pharmaceutical industry	126 (2.72)	41 (0.75)	3.68 (2.58-5.25)*
Government funding agent	91 (1.97)	45 (0.83)	3.25 (2.07-5.10)*
Academic institutions	1660 (35.87)	707 (13)	5.14 (4.59-5.76)*
Investigator initiated (self-funded)	394 (8.51)	190 (3.49)	8.60 (6.86-10.79)*
Miscellaneous sources of fund	300 (6.48)	76 (1.40)	9.08 (6.65-12.40)*
Not mentioned	116 (2.51)	41 (0.75)	5.17 (3.20-8.35)*

*$P<0.001$. OR=Odds ratio, CI=Confidence interval

lack of awareness of prospective registration. This was followed by lack of organization (28%) with lack of time, forgetfulness, and confusion about who was responsible for registering the study. A small proportion also did not realize the distinction between prospective submissions for registration versus receipt of final approval for registration. All of these reasons also likely apply to India and the last reason is particularly important as CTRI often raises queries that need to be addressed by the registrant prior to receiving the final registration number. If these queries raised by CTRI are missed or remain unanswered, the trial simply does not get registered.

Two key findings of our audit are as follows: (a) CTRI despite its mandate of prospective registration continues to permit retrospective registration and (b) A few regulatory studies continue to be retrospectively registered. The former is likely due to the fact that trial registration (even if retrospective) at least ensures registration and thus public access to studies. This is particularly true for regulatory studies. CTRI is also helping researchers (via continued retrospective registration) toward publication as many journals require trial registration prior to manuscript submission or acceptance.[7] The retrospective registration of regulatory studies is, however, more dangerous and represents a serious ethical and regulatory breach. Beyond awareness, one way to potentially minimize and even bring to zero retrospective registration is to link the ethics committee approval to the clinical trials registration (as seen in the United Kingdom from September 2013), with trial registration being a mandatory prerequisite for the final ethics committee approval.[8]

In summary, the implementation of prospective registration of studies by CTRI with effect from April 1, 2018, has led to a significant reduction in studies registered retrospectively regardless of their nature. However, some studies including some regulatory studies continue to be retrospectively registered. This can be addressed by linking CTRI registration with the ethics committee approval. With greater awareness, it is hoped that as a country, we will slowly but surely move towards zero retrospective registration of trials in the years to come.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Tharyan P, Ghersi D. Registering clinical trials in India: A scientific and ethical imperative. Natl Med J India 2008;21:31-4.
2. Pandey A, Aggarwal A, Maulik M, Challenges in Administering a Clinical Trials Registry: Lessons from the Clinical Trials Registry-India. Pharm Med 2013;27:83-93. https://doi.org/10.1007/s40290-013-0009-3.
3. Birajdar AR, Bose D, Nishandar TB, Shende AA, Thatte UM, Gogtay NJ. An audit of studies registered retrospectively with the clinical trials registry of India: A one-year analysis. Perspect Clin Res 2019;10:26-30.
4. Clinical Trials Registry-India (CTRI); 2020. Available from: http://ctri.nic.in/Clinicaltrials/login.php. [Last accessed on 2020 Mar 21].
5. WMA-The World Medical Association-WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. [Last accessed on 2020 Apr 02].
6. Hunter KE, Seider AL, Askie LM. Prospective registration trends, reasons for retrospective registration and mechanisms to increase prospective registration compliance-descriptive analysis and survey. BMJ Open 2018;8:e019983.
7. ICMJE Recommendations Clinical Trials. Available from: http://icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. [Last accessed on 2020 Apr 02].
8. Research Registration and Research Project Identifiers. Health Research Authority. Available from: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/. [Last accessed on 2020 Apr 02].