Original Article

An audit of studies registered retrospectively with the Clinical Trials Registry of India: A one year analysis

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Abstract

Background: The Clinical Trials Registry of India (CTRI) was launched in July 2007 and will enter its tenth year in 2017. While its mission is to encourage prospective trial registration, CTRI does permit retrospective trial registration. Against this backdrop, the present audit was carried out with the primary objective of assessing the nature and extent of trials retrospectively registered with CTRI.

Methods: All studies registered in the year 2016 were searched within CTRI using the keyword "CTRI/2016." The total number of trials registered in that year, their phase, the source of funding and their nature (Interventional or observational; whether postgraduate theses or otherwise, source of funding (pharmaceutical industry/Government of India/Institute Funded), whether prospectively or retrospectively registered were noted. We also tested for the association between the nature of the trial and retrospective registration using the Chi-square test and generated crude odds ratios with 95% confidence intervals.

Results: A total of 1147 studies were registered in 2016, of which 719 (63%) were retrospectively registered. Interventional studies formed the majority of studies at $n = 926$ (81%), while postgraduate theses constituted half of the studies (384; 53%). Postgraduate theses (relative to all other studies) were twice as likely to be retrospectively registered (cOR 2.4 [1.8, 3.0], $p < 0.0001$). Studies funded by the pharmaceutical industry were four times more likely to be registered prospectively relative to nonindustry funded studies (cOR 4.4 [3.2, 5.9], $p < 0.0001$).

Conclusion: Given that CTRI will be insisting on prospective registration effective April 1, 2018, and as trial registration is an ethical, scientific and moral imperative, prospective registration must always be done as prerequisite to participant protection.

Keywords: Funding source, lag time, medical devices, postgraduate theses, publication, trial registration

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INTRODUCTION

Registration of all clinical trials and interventional trials in particular is considered an ethical, scientific, and moral imperative.[1] Trial registration serves several purposes. The key among them include – (1) providing a public record of the trial (including its essential elements and information about key stakeholders), (2) identification

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of any discrepancies between the registered trial and the final published paper, (3) provision of information to both patients and healthcare providers about trials that they could potentially participate in, and (4) make available results of the study to potentially avoid publication bias.[2,3] Several editors of biomedical journals, including from India, endorse trial registration as a prerequisite to publication.[4,5]

A centralized and voluntary trials registry, the Clinical Trials Registry of India (CTRI) was launched in the country July 2007.[6] In June 2009, the Drugs Controller General of India (DCGI) made it mandatory for regulatory studies to be registered with the CTRI (office order F No 12–01/09-DC-[Pt 32]). The mission of the CTRI is primarily to ensure prospective registration of all clinical trials in India, i.e., before the recruitment of the first participant.[7] While prospective registration is ideal, in an attempt to encourage registration, the CTRI, at the moment does permit registration of trials that are ongoing or even completed (retrospective registration). Against this backdrop, the present audit was carried out with the primary objective of assessing the extent and nature of studies retrospectively registered with the CTRI in a one year period.

METHODS

Ethics

The study protocol was submitted to the Institutional Ethics Committee, who deemed it exempt from review as the data were available in public domain.

Study design, selection criteria, and study sample

The audit included all studies registered in the year 2016. The year was chosen as this was the last year where complete data would be available and also as CTRI would enter its tenth year in 2017. Thus, all studies registered in 2016 formed the study sample.

Search strategy

The website (www.ctri.nic.in) was searched using the keyword "CTRI/2016" to identify all studies registered in that year.

Outcome measures

The total number of trials/studies registered in 2016, their phase, (Phase I–IV); nature (interventional or observational; whether postgraduate theses or otherwise and source of funding (Pharmaceutical Industry/Government of India/Institute Funded) were noted. All of the above variables were similarly noted for studies that were registered retrospectively with the only addition being the "lag time" (time taken to register after enrolment of the first participant).

Statistical analysis

Both descriptive and inferential statistics were applied. Quantitative data were described using median (interquartile range) while categorical data were expressed as proportions. The association between the nature of the trial/study and retrospective registration was tested using the Chi-square test. In addition, a crude odds ratio along with 95% confidence intervals was generated. The following associations were derived-interventional versus observational studies, postgraduate theses versus the remainder of the studies and pharmaceutical industry-funded studies (regulatory studies) versus studies funded by other sources. All analyses were done using Microsoft Excel version 2010. (Microsoft Corporation, Redmond, Washington, U.S.A.) and a p-value of less than 5% was considered significant.

RESULTS

Demographics

A total of $N = 1147$ studies were registered with CTRI in 2016. Among these, $n = 719$ (63%) were retrospectively registered and the remainder $n = 428$ (37%) were prospectively registered. Interventional studies formed the majority of studies at $n = 926$ (81%) with the remainder being observational ($n = 221$, 19%). Postgraduate theses formed a little under half of the studies (524; 45.7%). A majority of the studies (703; 61.2%) were institutionally supported, while approximately, a quarter (245; 21.6%) was funded by the pharmaceutical industry.

The phase of the study was stated as "not applicable" in $n = 594$ records (51.8%). Of the remaining $n = 553$ records, there were $n = 47$ Phase I, $n = 43$ Phase I/II trials, $n = 100$ Phase II, $n = 36$ Phase II/III studies, $n = 123$ Phase III, $n = 16$ Phase III/IV, and $n = 188$ Phase IV/postmarketing surveillance (PMS) studies. A total of $n = 23$ studies involved medical devices. Details of the studies (including if they were registered retrospectively) are described in Table 1.

Analysis of all studies registered retrospectively

Of the $n = 719$ (63%) studies registered retrospectively, a majority were interventional (577/719; 80.2%). Postgraduate theses constituted half of the studies (384/719; 51%). Approximately three-fourths (477/719; 68%) studies were supported through institutional funding while 86/719 (12%) were supported by the pharmaceutical industry. There were $n = 24$ Phase I, $n = 25$ Phase I/II, $n = 75$ Phase II, $n = 23$ Phase II/III, $n = 55$ Phase III,

Table 1: Demographics of the *N*=1147 studies registered with clinical trials registry of India in 2016

Total number of studies (*N*=1147)	Retrospectively registered *n*=719/1147 (63%)	Prospectively registered *n*=428 (37%)
Classification of studies (percent)		
Observational *n*=221/1147 (19.3)	142/719 (19.7)	79/428 (18.5)
Interventional *n*=926/1147 (80.7)	577/719 (80.3)	349/428 (81.5)
Postgraduate theses *n*=524/1147 (45.7)	384/719 (53.4)	140/428 (32.7)
Source of funding		
Pharmaceutical industry funded studies *n*=245/1147 (21.4)	86/719 (11.9)	159/428 (37.1)
Studies supported by institutions *n*=703/1147 (61.3)	477/719 (66.3)	226/428 (52.8)
Investigator initiated studies *n*=85/1147 (7.4)	72/719 (10.0)	13/428 (3.0)
Government of India funded studies *n*=85/1147 (7.4)	63/719 (8.7)	22/428 (5.1)
Supported by nongovernmental Organizations *n*=21/1147 (1.8)	14/719 (1.9)	07/428 (1.6)
Source of support not mentioned *n*=08/1147 (0.7)	07/719 (0.9)	01/428 (0.2)

n = 13 Phase III/IV, and n = 103 Phase IV/PMS studies. The remaining n = 401 studies were marked as "phase not applicable."

Analysis of studies registered retrospectively that was supported by the pharmaceutical industry

Of the 86 studies that were supported by the pharmaceutical industry, drug studies were n = 15, medical device studies were n = 13, while CAM and others (e.g. toothpaste and mosquito repellant studies) made up for remaining n = 58 studies. When these n = 15 drug studies were further analyzed, we found the studies to be heterogeneous in nature – (a) n = 3 bioequivalence and/or pharmacokinetics, (b) n = 1 registry, (c) n = 4 postmarketing studies for safety/efficacy or both, (d) n = 1 Phase 1 study, (e) n = 5 Phase III, and (f) n = 1 Phase II/III study.

Further, we found that of these 86 pharmaceutical industry supported studies, n = 12 were regulatory in nature, i.e., initiated and funded by the pharmaceutical industry and requiring DCGI approval. Of these, n = 2 were Phase I, n = 1 Phase II/II, n = 4 Phase III, n = 1 Phase III/IV, n = 1 Phase IV, and n = 3 were "Phase not applicable." The remaining n = 68 were nonregulatory, i.e., either investigator initiated with support from the pharmaceutical industry or studies by the pharmaceutical industry not needing DCGI approval, and n = 6 studies were divided into n = 4 studies "notified to DCGI" and n = 2 "awaiting approval" and "no objection certificate received" each.

Analysis of lag time for retrospectively registered studies

The median (range) time to retrospective registration of the n = 719 studies was 428 (1–5399) days with the interquartile range being 220–868 days. Of the n = 86 studies that were supported by the pharmaceutical industry, the median lag time to registration was 192 (3–3794) days. Of the n = 18/86 studies that were regulatory in nature, the lag time ranged was 131.5 (3–2000) days.

Analysis of association between the type of registration (prospective or retrospective) and nature of studies

When studies were divided as interventional or observational, no association was seen with regards to type of registration ($p > 0.05$). Postgraduate theses (relative to all other studies) were twice as likely to be retrospectively registered ($p < 0.0001$; cOR 2.4 [1.8, 3.0]). Studies funded by the pharmaceutical industry were four times more likely to be registered prospectively relative to nonindustry funded studies ($p < 0.0001$, cOR 4.4 [3.2, 5.9]). Studies that involved medical devices (relative to other pharmaceutical industry-funded studies) were three times more likely to be registered retrospectively ($p < 0.038$; cOR 2.76 [1.1, 6.3]).

DISCUSSION

The present study, an audit of registered trials in CTRI for the year 2016 shows that almost two-thirds studies are registered retrospectively with a vast majority of them being interventional trials; a disconcerting finding.

We found a lag time in our study for retrospectively registered studies to range from as low as 1 day to as high as 15 years. The single day's delay is likely an index of forgetting to register on time and then remembering almost immediately, while the larger delays can have multiple reasons. One potential reason is journal editors' insisting on trial registration (albeit retrospective). Harriman and Patel in their study on n = 108 trials published in the BioMed Central series (2013) found that only 31% trials were registered prospectively, 67% trials were registered retrospectively, and 2% trials did not report a trial registration number. Of the studies registered retrospectively (n = 72), 92%

were registered just before manuscript submission and 8% after submission indicating that need for the journal to have a registration number in the published paper seems to be the only driving force behind trial registration.[8] Subsequent to our planned analysis, we attempted to see if some of the retrospectively registered trials were in fact published. We searched PubMed and Google Scholar for publications pertaining to the n = 719 studies registered retrospectively and found n = 89 published papers. In n = 76/89 papers, the registration preceded the publication. This finding is similar to that of Harriman and Patel and lends credence to the fact that journal editors may have insisted on trial registration or accepted for publication a trial/study that was retrospectively registered. Some studies were initiated before CTRI was established and these too have been registered retrospectively and could explain the 15 years lag seen.

In n = 13 papers, the publication preceded the date of CTRI registration. While we are unable to explain why the trial/study registration was done subsequent to the publication, it may reflect an apathetic approach toward the process of registration. When finally done, it was likely done as an administrative exercise for closure. None of the 13 low supports among investigators for trial registration has previously been noted. A survey in 2007 found that only 21% of respondents had registered all ongoing trials since 2005 and only 47% stated that they would register future clinical trials.[9] The same survey also found that "lack of time to complete bureaucratic tasks" to be a common theme among the respondents. Creating awareness about the need for trial registration and its benefits as also journal editors insisting on prospective registration could represent two potential modalities to address this apathy.

The delay in registering regulatory studies represents a serious violation of the country's regulatory mandate. We found at least 12 regulatory studies that were registered retrospectively in violation of the country's laws. One of these was a Phase I study with a novel vaccine. This challenge can only be addressed through strict implementation of prospective registration, both by the regulator and the Ethics Committees that approve these studies. In addition, the manner in which information within CTRI is filled often makes it difficult to determine whether a study is truly regulatory in nature and the pharmaceutical industry, in particular, must fill in CTRI requirements with attention to detail which must also be verified by the CTRI.

We found that when the source of funding was from the pharmaceutical industry, the trials were four times more likely to be prospectively registered, while postgraduate theses were twice as likely to be retrospectively registered. The former finding is similar in part to that of Scott *et al*. who found in their study of five psychiatry journals that mandate prospective trial registration that prospective registration of trials (along with no changes to outcome measures) was more likely to occur with regulatory studies.[10] The latter finding though is disconcerting. The reasons could be lack of awareness and apathy, uncertainty about whether a thesis merits registration and the possible need to change primary outcomes of the thesis posttrial registration (as the study progresses or if the thesis was hypotheses generating). Nonetheless, prospective registration will remain the fundamental responsibility of both the student and the supervisor.

Some responsibility of the lack of "on time" registration of trials also needs to be borne by the institutions and Institutional Ethics Committees who approved these studies as three quarters of the retrospectively registered trials in our study received intramural funding. One way that international electronics and communication systems (IECs) can insist on prospective registration is to have a declaration for prospective registration in the IEC submission form[11] and following it up during the IEC monitoring process.

Our study found that of the n = 23 medical device studies, n = 13 were registered retrospectively with a large majority of them being Phase IV/PMS studies. The draft medical devices rule of October 17, 2016, has been notified by the Health Ministry on January 31, 2017.[12] Among the n = 15 medical devices listed therein, n = 8 devices are regulated as "Drugs" and thus studies with all of these 8 must undergo prospective trial registration in future. This is something device manufacturers' need to bear in mind.

This study is limited by the fact that it covered a single year only; and thus, a trend analysis was not possible. Furthermore, individual trialists were not contacted to ascertain-specific reasons for retrospective registrations. The unplanned analysis regarding publications was also restricted to only two databases.

CONCLUSION

This study highlights the need to create awareness about trial registration and its benefits, dispelling uncertainty among the minds of researchers/trialists/postgraduate teachers about the need for registration and the importance of registering theses particularly when they are interventional studies. This is now more important than ever as effective April 1, 2018, CTRI will accept studies only if they are prospectively registered[7] and this will have far-reaching implications. It will include failure to publish valuable

evidence if journal editors also begin to insist on both registration and prospectively registered trials. The most recent version of the Declaration of Helsinki (2013) also mandates prospective registration of any research study.[13] Prospective registration thus must always be done as an essential imperative for participant protection.

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Conflicts of interest

There are no conflicts of interest.

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