Registering clinical trials in India: A scientific and ethical imperative

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ABSTRACT

The Clinical Trials Registery–India is an online, primary register of the WHO's International Clinical Trials Registry Platform. It was launched on 20 July 2007, and is now open to the prospective registration of clinical trials of any intervention conducted in India involving human participants. Registration is voluntary and free, and the register is searchable free of charge. Public disclosure of all 20 items in the WHO Trial Registration Data Set is mandatory for a valid registration number to be allocated. This number is required if the results are to be published in journals that endorse the International Committee of Medical Journal Editors' position on prospective trials registration. Trials in the Clinical Trials Registery–India will be included in the central repository of the WHO's International Clinical Trials Registry Platform search portal. In addition to the 20 items, the Clinical Trials Registery–India also requires mandatory disclosure of details of ethics committee and regulatory clearances. Further items pertaining to the methods that improve the internal validity of the trial are optional and serve as a template to improve trial design and the reliability of results. The success of this endeavour depends on the cooperation of the pharmaceutical industry, academic institutions, medical associations, ethics committees and medical journal editors in India. In the absence of legislation, ethics committees and medical journal editors have an important role in ensuring prospective registration of trials.

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INTRODUCTION

On 20 July 2007, the Clinical Trials Registry–India (CTRI; *http://www.ctri.in*) was launched at the National Institute of Medical Statistics, New Delhi. With this launch, India announced to the international community its intention to make crucial information about clinical trials conducted in India publicly available. By insisting on the registration of all 20 items in the WHO Trial Registration Data Set (Table I) and additional CTRI-specific items (Table II), the CTRI will hopefully be able to influence and strengthen the design, ethical conduct and eventual reporting of clinical trials. The launch also signified India's endorsement of the WHO position that registration of clinical trials is a scientific, ethical and moral imperative.

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THE CLINICAL TRIALS REGISTRY–INDIA

Shortly after the launch, the WHO's International Clinical Trials Registry Platform (WHO ICTRP; *http://www.who.int/ictrp*) designated the CTRI as a primary register in its network of registers thus ensuring that data regarding trials registered in the CTRI will be displayed in the WHO ICTRP search portal.[1] Currently, there are 3 other primary registers in the WHO ICTRP network: The Australian New Zealand Clinical Trials Registry; the Chinese Clinical Trials Register (launched on 25 July 2007) and the International Standard Randomized Controlled Trial Number Register. Although not a primary register, data from *ClinicalTrials.gov* will also be included in the WHO search portal.

As a WHO primary register all trials that are fully registered in the CTRI will also meet the registration requirements of the International Committee of Medical Journal Editors (ICMJE), which recently supported the efforts of WHO to provide a one-stop search portal for those seeking information about clinical trials.[2] This endorsement by the ICMJE of the WHO registry platform is important since their policy, initiated in 2004, requires prospective registration and full disclosure of all 20 items in the WHO Trial Registration Data Set (Table I) before enrolment of the first participant, as a mandatory prerequisite for the trial's results to be considered for publication by many major international journals.[3,4]

The CTRI will accept registration from individual registrants as well as from other registers (Partner Registers that may have a specific focus, e.g. registers of some pharmaceutical companies)

TABLE I. World Health Organization–International Clinical Trials Registry Platform (WHO ICTRP)/International Committee of Medical Journal Editors (ICMJE) minimal registration data set*

No.	Item
1	Primary register and trial ID # (unique trial number)
2	Date of registration in primary register (trial registration date)
3	Secondary IDs
4	Source(s) of monetary or material support (funding source(s))
5	Primary sponsor
6	Secondary sponsor(s)
7	Contact for public queries (responsible contact person)
8	Contact for scientific queries (research contact person)
9	Public title (title of the study)
10	Scientific title (official scientific title of the study)
11	Countries of recruitment (research ethics review)†
12	Health condition(s) or problem(s) studied (condition)
13	Intervention(s)
14	Key (a) inclusion and (b) exclusion criteria
15	Study type
16	Date of first enrolment (anticipated trial start date)
17	Target sample size
18	Recruitment status
19	Primary outcome(s) (primary outcome)
20	Key secondary outcomes

* The WHO ICTRP Registration data set (from *http://www.who.int/ictrp/data_set/en/*) and differences in the terminology in the ICMJE minimal registration data set[4] (in parentheses) † Originally 'Research ethics review' in the WHO ICTRP registration data set but subsequently replaced by 'Countries of recruitment'

TABLE II. Registration data set in Clinical Trials Registry–India (CTRI)

No.	Item	Comments
1	UTRN	Universal trial reference number. (This field is currently disabled as the UTRN is being developed and piloted.)
2	CTRI number	Equivalent to item 1 in Table I; will be assigned by the CTRI once trial details are verified till which time only a temporary number will be assigned
3	Date of registration in CTRI	Equivalent to item 2 in Table I; will be assigned by the CTRI after verification
4	Title of study*	Equivalent to item 9 in Table I
5	Scientific title of study*	Same as item 10 in Table I
6	Secondary IDs, if any	Equivalent to item 2 in Table I; refers to registration ID of another primary register for multi-country trials conducted in India but also accommodates other identification numbers such as sponsor's protocol numbers, registration numbers of other registers, etc.
7	Principal investigator or overall trial coordinator (multi-centre study) name and contact details	CTRI specific item
8	Contact person (scientific query)	Equivalent to item 8 in Table I
9	Contact person (public query)	Equivalent to item 7 in Table I
10	Source/s of monetary or material support	Same as item 4 in Table I
11	Primary sponsor	Same as item 5 in Table I
12	Secondary sponsor	Same as item 6 in Table I
13	Countries of recruitment	Same as item 11 of the WHO registration data set in Table I
14	Site/s of study	CTRI-specific item
15	Name of ethics committee and approval status*	CTRI-specific item but similar to item 11 of the ICMJE minimal registration data set in Table I, not required by WHO.
16	Regulatory clearance obtained from the Drug Controller General of India*	CTRI-specific item
17	Brief summary	CTRI-specific item
18	Health condition/problem studied	Equivalent to item 12 in Table I
19	Study type	Same as item 15 in Table I
20	Intervention and comparator agent	Equivalent to item 13 in Table I
21	Key inclusion/exclusion criteria	Same as item 14 in Table I
22	Method of generating randomization sequence	CTRI-specific item
23	Method of allocation concealment	CTRI-specific item
24	Blinding and masking	CTRI-specific item
25	Primary outcome/s	Same as item 19 in Table I
26	Secondary outcome/s	Same as item 20 in Table I
27	Target sample size	Same as item 17 in Table I
28	Phase of trial*	CTRI-specific item
29	Date of first enrolment	Same as item 16 in Table I
30	Estimated duration of trial	CTRI-specific item; requires the expected time duration of trial, starting from enrolment of first patient
31	Status of trial *	Same as item 18 in Table I

ID Identification details * mandatory CTRI items (some specific to this registry) required for registration to proceed to completion

for registering trials conducted in India. The CTRI will register trials free of charge and will also be searchable via the internet for free. It will collect and display the WHO Trial Registration Data Set and also identify trials that do not provide the complete WHO Trial Registration Data Set at the time of initial registration by assigning them a temporary CTRI registration number. Trials once registered will not be removed and any changes made to the WHO Trial Registration Data Set will be tracked via a publicly accessible audit trail. Multi-country trials with any recruitment site(s) in India are expected to prospectively register the India-specific details in the CTRI, even if the trial is registered in another register. The CTRI will ensure that a single trial is not registered more than once in its registry and will identify trials registered in other registers by requesting that the trial identification numbers allocated by other registers are also entered in the data set submitted. The WHO search portal (and the other primary registers, if necessary) will also be searched in an effort to ensure that trials registered elsewhere are identified. Once the mandatory items required for registration are completed and the trial registered in the CTRI, the WHO Trial Registration Data Set will be transferred to the WHO ICTRP central repository and these details will then be searchable through the WHO ICTRP search portal (*http://www.who.int/trialsearch/*).

The CTRI is currently accepting registration of trials conducted in India but it hopes to upscale its remit to allow trials conducted in other countries in the region to be included. It is managed by the National Institute for Medical Statistics, a not-for-profit government organization, and has a Steering Group and a Technical Advisory Group. It is working on standard operating procedures (SOPs) for registering trials and will participate with the WHO ICTRP network of registers in the development of Guidelines for Clinical Trials Registers. The CTRI is also working with the WHO ICTRP in developing and piloting a system for assigning a Universal Trial Reference Number (UTRN) that will, in the long term, aid the unambiguous identification of all trials. When implemented, the UTRN can be obtained by the trial's sponsor or principal investigator from the WHO ICTRP website early in the trial's history. The UTRN will then become part of the trial's international identity along with the CTRI registration number (and other identification numbers of primary registers for multi-country trials).

PROSPECTIVE REGISTRATION OF CLINICAL TRIALS

A scientific and ethical imperative

Scientific knowledge is cumulative. For clinical decisions to be adequately guided by reliable evidence, data from all clinical

trials need to be available, not only data from trials that were written up and submitted for publication, or those that journal editors decided to publish[4] (usually because the results were interesting, though not necessarily complete). Many high-profile examples of selective reporting (for example, failure to report all adverse events) and the results of empirical research demonstrating both the existence of publication bias and discrepancies in reporting outcomes between trial protocols and published reports[5,6] led to calls for prospective registration of clinical trials and publication of detailed clinical trial protocols.[2–4,7] While the Ottawa Statement[7] calls for registration of the complete trial protocol as well as any amendments, the WHO and ICMJE requirements currently stop short of this. The 20-item Registration Data Set (Table I) is considered the minimum information required to be able to identify a trial and disclose crucial details of its objectives and methods, outcomes and funding sources.

However, the fundamental and overarching reason to prospectively register trials and disclose important details is the ethical obligation to trial participants, who are subjected to potential personal risks in exchange for the accumulation of public scientific knowledge. If the existence of a clinical trial and its results remain unknown to anyone but the trial investigators then it could be argued that the trial is unethical. Trials registers are also used by patients and healthcare providers to identify clinical trials they may wish to participate in, and have other potential uses for policy-makers and funding agencies in research priority setting, resource utilization and capacity building for research, as well as for everyone involved in informed healthcare decision-making.[8]

CAN TRIAL REGISTRATION IMPROVE THE DESIGN, INTERNAL VALIDITY, ETHICAL CONDUCT AND REPORTING OF CLINICAL TRIALS FROM INDIA?

Empirical research from India (unpublished data) reveals that a large proportion of randomized clinical trials published in Indian medical journals fall short of the international reporting standards set by the Consolidated Standards for Reporting Trials (CONSORT) statement and the uniform requirements of the ICMJE.[9,10] Particularly disconcerting is the inadequate reporting of critical elements of trial design that impact on the internal validity of randomized controlled trials such as concealment of allocation of the randomization sequence and details of who among participants and the investigating team were blinded (unpublished data). Poor reporting may stem from poor research design resulting from inadequate appreciation of the sources of bias in clinical trials and of the methods available to improve internal validity. In such instances attempts to comply with CONSORT requirements (even if mandated by editorial policy of the journals), at the time of reporting results may be too late, as these elements need to be considered when trials are designed. Recruiting participants in clinical trials that are likely to produce unreliable results is surely unethical.

The CTRI data set includes three items pertaining to internal validity that do not form part of the 20-item WHO Registration Data Set. Registrants are requested (though not mandated as yet) to describe the method used for generation of the random sequence, method used to conceal allocation to interventions, and exactly who will be blinded to interventions (Table II). The drop down menu of options and a downloadable explanatory document provide educational opportunities to help prospective trialists improve the design of the trial at the stage of registration and consequently improve the reliability of the trial's results. It is hoped that, in time, these optional items in the CTRI will lead to better reporting of methods of the trial that impact on trial outcomes[11] and would address concerns about trials from countries such as India (and China), where the tremendous growth in the number of clinical trials being conducted has been matched by the growth in criticism of the ethical conduct and reliability of results.[12,13] However, for this strategy to work, trial protocol submissions to ethics committees would also have to be modified to include items pertaining to the internal validity of the trial.

In addition to the mandatory 20-items of the WHO Data Set that are required to be disclosed before a permanent, and valid, CTRI registration number is assigned that meets the WHO ICTRP and ICMJE requirements, the CTRI has register-specific items that need to be disclosed before registration can proceed to completion (Table II). One of these requires the names of all ethics committees from whom approval has been sought to be disclosed, the approval status at the time of registration, and a copy of the approval letter(s), when available. The register also seeks disclosure of clearance from the Drug Controller General of India (for trials that require this) and a copy of the clearance letter. This information is being collected as it cannot be presumed that ethics approval has been obtained for all trials conducted in India or other developing countries[14] and mandatory disclosure of the specific ethics committee that cleared the trial as well as proof of this approval may lead to more responsible conduct and supervision of the trial.

ENCOURAGING COMPLIANCE WITH TRIALS REGISTRATION

Although a trials register can provide a template for better trial design, it cannot fully ensure that all trials will be registered, that meaningful data will be submitted, or that full disclosure of all items will result. The CTRI will attempt to clarify incomplete or inadequate registry submissions with registrants, verify registration details with responsible people in the host institutions and will label verified and unverified trials in the registry. Additional methods to encourage compliance and full disclosure could include the periodic publication of reports of details of trials registration in the CTRI, and naming of defaulters, as was so successfully demonstrated by *ClinicalTrials.gov*.[15] Registration on the CTRI of trials conducted in India will, for the moment, remain voluntary. Compliance will therefore depend on the cooperation of the pharmaceutical industry and contract research organizations, academic institutions, medical associations, ethics committees and medical journal editors in India. Dialogue with all stakeholders has commenced and will continue. The ICMR's initiatives to build capacity in India for the responsible conduct of clinical trials,[16] and that of the Drug Controller to audit the conduct of clinical trials,[17] are additional methods being initiated to create a responsible research environment that could auger well for trials registration.

When the efforts of the Study Group on the Reporting of Findings of Clinical Trials constituted by the WHO ICTRP leads to globally acceptable mechanisms that result in the timely public reporting of all the results of registered trials, the cycle initiated by the ICMJE and Ottawa Statements[3,7] would be complete and the CTRI will expand its scope to include these recommendations as well.

There are those who believe that trials registration should be made mandatory by law. In February 2007, a Bill was passed by the US Congress called the Fair Access to Clinical Trials Act (FACT).[18] This Bill requires the US Food and Drug Administration (FDA) to expand the *ClinicalTrials.gov* database to create a

publicly accessible national data bank comprising a clinical trial registry and a clinical trial results database. The Bill further requires all trials to be registered in the database in order to obtain approval from US Institutional Review Boards and requires the FDA to make internal drug approval and safety reviews publicly available. An associated bill was subsequently passed by the US House of Representatives and in September 2007, the two were reconciled and signed into law as the Food and Drug Administration Revitalization Act.[19] This Act echoes important elements of the WHO ICTRP and ICMJE positions on prospective trials registration. It also endorses the ICMJE position on reporting results of registered trials[2] and the activities of the WHO ICTRP's Study Group on the Reporting of Findings of Clinical Trials by mandating the reporting of results (information on trial participants, and primary and principal secondary outcomes) in a publicly available database.

The ICMR has published ethical guidelines for biomedical research in India[20] but legislation to enforce these guidelines is still pending. In the absence of legislation, it is important that medical journal editors and ethics committees become actively involved in the registration of trials;[21] no legislation is required for this. Since the CTRI requires proof of ethics clearance before registration, ethics committees could approve protocols pending registration but require that no subjects be enrolled in a trial without a valid CTRI registration number.[22] The ICMR ethical guidelines also need to be updated to include prospective registration of trials as a scientific and ethical requirement and assign ethics committees the role of ensuring valid prospective registration. Medical journal editors could serve as additional gate-keepers and endorse the ICMJE position on prospective trials registration as a prerequisite for considering manuscripts of clinical trials for publication. This should be incorporated in the instructions to authors as part of the editorial policy of all medical journals in India and a date declared in editorials after which no trials conducted in India will be considered for publication in Indian medical journals that have not been registered in the CTRI.

CONCLUSION

Prospective registration of clinical trials is a welcome development in the ongoing saga of mankind's efforts to balance the accumulation of scientific knowledge with protecting the interests of trial participants. The CTRI data set fulfils the requirements of the WHO ICTRP and the ICMJE, and includes additional elements aimed at aiding the valid design, ethical conduct and eventual reporting of clinical trials. Registration is currently voluntary and, in the absence of legislation mandating prospective trials registration, medical journal editors and ethics committees have a special role in ensuring compliance with registration of trials and full disclosure.

The outcome of the debate in India on whether registration of trials should be made legally mandatory will largely depend on the progress made in the years to come in the voluntary registration and full disclosure of the required details in the CTRI of clinical trials conducted in India.

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