Journal of Evidence-Based Medicine ISSN 1756-5391

# Prospective Registration of Clinical Trials in India: Strategies, Achievements & Challenges

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**Keywords**
Clinical trials; research design; legislation; publication bias; Institutional Review Board

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Received 21 January 2009; accepted for publication 23 January 2009.

doi: 10.1111/j.1756-5391.2009.01015.x

## Abstract

**Objective** This paper traces the development of the Clinical Trial Registry-India (CTRI) against the backdrop of the inequities in healthcare and the limitations in the design, conduct, regulation, oversight and reporting of clinical trials in India. It describes the scope and goals of the CTRI, the data elements it seeks and the process of registering clinical trials. It reports progress in trial registration in India and discusses the challenges in ensuring that healthcare decisions are informed by all the evidence.

**Methods** A descriptive survey of developments in clinical trial registration in India from publications in the Indian medical literature supplemented by firsthand knowledge of these developments and an evaluation of how well clinical trials registered in the CTRI up to 10 January, 2009 comply with the requirements of the CTRI and the World Health Organization's International Clinical Trial Registry (WHO ICTRP).

**Results** Considerable inequities exist within the Indian health system. Deficiencies in healthcare provision and uneven regulation of, and access to, affordable healthcare co-exists with a large private health system of uneven quality. India is now a preferred destination for outsourced clinical trials but is plagued by poor ethical oversight of the many trial sites and scant information of their existence. The CTRI's vision of conforming to international requirements for transparency and accountability but also using trial registration as a means of improving trial design, conduct and reporting led to the selection of registry-specific dataset items in addition to those endorsed by the WHO ICTRP. Compliance with these requirements is good for the trials currently registered but these trials represent only a fraction of the trials in progress in India.

**Conclusion** Prospective trial registration is a reality in India. The challenges facing the CTRI include better engagement with key stakeholders to ensure increased prospective registration of clinical trials and utilization of existing legislative opportunities to complement these efforts.

## Introduction

With the launch, on 20 July 2007, of the Clinical Trial Registry–India (CTRI; *http: //www.ctri.in*) at the National Institute of Medical Statistics, New Delhi, India joined those in the international community that had long dreamt that crucial information about clinical trials conducted globally should be made publicly available for scientific and ethical reasons (1–4). The CTRI is a Primary Registry of the World Health Organization's International Clinical Trial Registry Platform (WHO-ICTRP) and meets specific criteria for content, quality and validity, accessibility, unique identification, technical capacity and administration (5). As a member of the WHO's list of Primary Registries, the CTRI also meets the requirements of the International Committee of Medical Journal Editors (ICMJE)

regarding registering clinical trials as a pre-requisite for consideration of publication in the ICMJE member journals (2). There are many reasons why the launch of the CTRI is important for research and healthcare in India and for changing international perceptions regarding research in India.

## Objective

This paper first discusses the issues peculiar to healthcare delivery and regulation of research in India in general, and clinical trials in particular; and the scientific and ethical imperatives that underpin clinical trial registration in India, which differ in some respects from the situation that prevails in many high income countries. It then traces the development of the mission and vision of the CTRI and trial registration dataset items additional to those in the WHO ICTRP 20-item minimum trial registration dataset (6). I detail the strategies that have shaped and accompanied its rollout and implementation; the progress with trial registration to date; and ends with a discussion on the continuing challenges India faces in ensuring transparency and accountability in research involving clinical trials in human participants.

## Methods

The material for this paper comes from relevant publications on trial registration gathered by ongoing electronic searches of consecutive issues of online Indian Medical Journals as part of the activities of the South Asian Cochrane Network & Centre (www.cochrane-sacn.org) to develop a database of controlled clinical trials conducted in South Asia (www.cochrane-sadcct.org), knowledge of the workings of the CTRI as a member of the Steering and Technical Working Groups of the CTRI and membership of the erstwhile Scientific and Advisory Group of the WHO ICTRP. Details salient to this paper's purview are presented from an analysis of the first 155 clinical trials registered in CTRI (search term CTRI; search date January 10, 2009).

## Results

### *Perspectives on health care and clinical research in India pertinent to clinical trial registration*

#### *Health care in India*

Although India is often touted as an Asian Tiger with an enviable growth rate that seems immune to the current financial meltdown, India lags behind many parts of the world on important healthcare indices. With a population of over one billion people, the public health system is unable to meet the healthcare needs of the entire population and only 20% of healthcare expenditure is met though government spending. The public health system has limited reach and is plagued by unregulated delivery, sub-standard facilities and malpractices. Most users of healthcare pay from their own pocket and, even in rural areas, prefer private services to government ones (7,8). These out of pocket expenses exacerbate poverty and constitute a prime reason for penury in the economically disadvantaged in India (7–9).

India has a very low density of doctors. The country has only 43 doctors for every 10,000 people, in spite of producing around 30,000 medical graduates every year from over 300 medical colleges across the country. There is a huge shortage of hospital beds. India has only 1.5 beds per 1000 population, similar to the situation in sub-Saharan Africa. At 0.9 nurses per 1000 population, India has even fewer nurses than sub-Saharan Africa that has 1.6 nurses per 1000 population (10).

India spends a high proportion of its gross domestic product (GDP) on health care but health outcomes are still poor as compared to countries at a similar level of development. Infant mortality (as an indicator) is high in India. On average, 55 out of every 1,000 children die (11). Life expectancy in India was amongst the lowest in the world, at 55.5 years in 2001 (10), though this had risen to 63.1 years in 2008 (11).

However, India also has a large middle class and a profitable private healthcare system consisting of state of the art 'corporate hospitals', private clinics and charitable, non-governmental institutions that provide health care to the majority of the population from urban and rural areas. There is also a large market for indigenous systems of medicine (Ayurvedha, Siddha & Unani) practised out of government-funded institutions as well as by private practioners. Primary care is provided largely by the private sector, with the government run Primary Health Centres often lacking adequate staff or medicines. Secondary care is fragmented with many private clinics run by individuals who also manage their own diagnostic laboratories or who get a commission from referrals to privately run laboratories. Tertiary care is available free of cost from Government hospitals but varies in quality across states and is hampered by large waiting lists. Tertiary care of excellent quality is largely provided by private, multi-speciality hospitals, though the expense involved puts such care out of the reach of many economically disadvantaged people. The cost of care is relatively low compared to prices overseas and India is seeing an influx of 'medical tourism' from many other countries. Affordable good quality tertiary care is also provided by many hospitals managed as charitable institutions or trusts. The private sector is largely unregulated (10).

#### *Health insurance*

Private insurance schemes cover less than 0.5% of the population. Mandated wage-based contributions from employers

and employees to the social insurance scheme cover an additional 3.5%. Employer's reimbursements for health care expenses or access to their facilities are available to around 5% and social insurance schemes run by non-governmental agencies cover an additional 5% of the population. This leaves about 85% of the population without health insurance (10). In 2005, the Indian Health Ministry announced an ambitious programme to bridge the urban-rural inequities in health care, the National Rural Health Mission that, among other commitments, aims to raise the annual spending on health care to more than 2% of GDP, from 0.9% in recent years, and to increase staffing levels in primary health centres (11,12). A micro-insurance scheme to cover the 35% of the population below the poverty line has also been announced, but the benefits of these schemes are yet to be formally assessed.

### *Healthcare regulation*

The Central Government's Ministry of Health and Family welfare frames health policies and is involved with the regulation of the healthcare industry and management of Public Health initiatives and facilities. However, the implementation of health policies and delivery of services is the responsibility of State Governments though their Ministries of Health. Considerable variations exist between states within India on the quality, reach and management of public health facilities. The Indian Medical Council is responsible for the licensing and regulation of all medical professionals but is largely uninvolved with the delivery of care or setting of standards of healthcare delivery. India has the dubious distinction of being the only nation where medical practice comes under the jurisdiction of the Consumer Protection Act (COPRA) (13).

### *Clinical trials and clinical research*

Interestingly, against this backdrop of inequity in access to health care, India has become a favoured destination for industry-sponsored international clinical trials. This is largely due to its English-speaking medical workforce, relaxed regulatory environment, considerably reduced costs for conducting clinical trials, lack of consumer participation in health-care decision-making, a relatively low frequency and magnitude of litigation and compensation claims, and its enormous, genetically-diverse, drug-naive population (14). Investigator initiated clinical research and clinical trials are also undertaken in many research and teaching medical institutions across the country. The ICMR has published ethical guidelines for biomedical research in India that is comparable with similar guidelines in other countries (15). However, the application of these guidelines in the over 300 institutional or independent ethics committees has not been formally assessed. Approval from the Drug Controller General of India is necessary for all new drugs and devices that are to be marketed in India and for new indications for existing drugs. Schedule Y of the Drugs and Cosmetics Act and Rules provides regulatory guidance on the conduct of all clinical trials involving drugs or devices in India (16). However, limitations in the provisions of the Act have prevented efffective enforcement of the provisions. Additional legislation to amend the Drugs and Cosmetics Act and provide for punitive actions from non-compliance and better regulate the conduct of clinical research in India is currently pending legislative approval (17).

The lack of regulatory jurisdiction over the numerous private sites that are increasingly being used for multi-country trials facilitates recruitment to trials. The lack of a national ethics body with regulatory powers permits sloppy ethical safeguards. These factors create conditions that can lead to the poor conduct of clinical trials. Recruiting participants is also easy since informed consent is freely given when research is combined with (and mistaken for) routine care and the process of informed consent is subverted to a single event, without any independent verification of this event. The twin incentives of a foreign drug and free treatment are often all that are needed to ensure participation, considering the reality of inequity in access to affordable and good quality care. Protocols and procedures do not require validation or review of consent. The lack of clinical ethics teaching in most medical schools and the lack of clinical ethics committees, separate from research ethics committees, in most medical schools results in the uneven development of the procedural safeguards for clinical research that should normally flow from the procedural safeguards for good practice in clinical care (18). Concerns have also rightly been raised regarding the use of third world countries for what are seen as trials whose results would mainly benefit people living in the developed world, and of the lack of ethical oversight of such trials (18,19).

Medical journal editors have multiple responsibilities that include safeguarding the rights of participants, establishing policies of submission, review and acceptance of manuscripts, and working towards improving the quality of the conduct and publication of research (20). However a survey of instructions to authors and an analysis of reporting standards against the Consolidated Standards of Reporting Trials (CONSORT) statement (21) guidelines and ICMJE requirements (22) in 65 online Indian medical journals revealed considerable deficiencies in editorial requirements and oversight on reporting crucial issues of trial design that affect validity and interpretation of results, ethical oversight and disclosures of financial conflicts of interest (23).

Developing mechanisms and implementing prospective registration of clinical trials in India needs to be framed within these perspectives and the sections that follow will attempt to address these concerns while tracing the evolution and progress of the CTRI.

### The evolution of the Clinical Trial Registry-India (CTRI)

India's formal involvement with clinical trial registration began with the inclusion of the former Director General of the Indian Council of Medical Research (ICMR), as a member of the International Advisory Group of the WHO-ICTRP, though attention had been drawn earlier on the need for India to join the ICMJE initiative on prospective trial registration as a pre-requisite to consideration for publication (24). This involvement led to the formation of a steering group to develop the terms of reference and the elements of an Indian registry and the drive towards developing this registry to comply with the requirements of the WHO-ICTRP to become a Primary Register of the ICTRP's network of registers (5). The ICMR has also been represented at meetings of the WHO-ICTRP's Registers Working Group by senior officials who have translated their involvement to the deliberations and workings of the Steering and Technical Advisory groups of the CTRI.

### The mission and vision of the CTRI

From the outset it was thought important to utilise the opportunity of designing the CTRI to achieve more than compliance with international requirements for transparency in clinical research. The results of the survey on editorial policy suggested that the deficiencies in reporting the results of clinical trials in Indian medical journals could be due to poor understanding of the importance of complete reporting of elements of trial design pertaining to minimizing bias and improving internal validity (23). Equally possible was the notion that poor reporting could be due to poor study design. Also worrying was the poor reporting of ethical safeguards, funding sources and conflicts of interest.

The implications of these findings on reporting of trials in Indian journals have a direct bearing on evidence–informed health care in India. Systematic reviews of good quality randomized trials form the highest level of evidence for the effects of interventions in healthcare. Inclusion of trials of good quality from resource-constrained settings such as India would help in generalizing the results of systematic reviews to healthcare in these settings. Publishing trials of poor quality could lead to erroneous results, if included in systematic reviews (25), or their exclusion from such reviews could severely limit any discussion of the relevance of the review's findings to local clinical practice (23). Recent controversies regarding the ethical conduct of trials in India also mandated that trial reports are transparent about the ethical safeguards employed, sources of funding and conflicts of interest (18,19,25–27).

Improving the quality of conduct and reporting of locally relevant research in order to generate reliable evidence that would enable the appropriate use of scarce resources, especially in resource-constrained settings such as India, and to better safeguard participants, was considered a necessary role for the CTRI. Hence, separate mission and vision statements were developed to reflect its scope (Table 1).

### The need for a separate national/regional trial registry

During the development of the CTRI, and even subsequently, questions were raised as to the necessity for multiple trials registers around the world when all trials could be registered in established trials registries. One concern was that this could lead to duplicate registration of the same trials that, if left unchecked, could compromise the integrity of trial registries by falsely over-inflating the number of trials and confusing users. Some proposed limiting the number of registries as a possible mechanism to prevent duplicate trial registration (28).

The need for separate national and regional registers, however, is based on necessity; the necessity to ensure political ownership of the process of trial registration and enhance transparency and accountability in research. National registers are also ideally placed to promote, identify and track clinical trials being conducted in a specific country, and are able to fully integrate into local ethics and regulatory processes thus ensuring complete and comprehensive registration of all trials conducted in their region of influence (29,30). Many multi-country trials registered in international registers in the home country of the sponsors do not provide details of the sites in India where trials are being conducted and reliance on only these registers

**Table 1** Mission and Vision of the Clinical Trial Registry-India (CTRI)

| | |
|---|---|
| Mission | To encourage all clinical trials conducted in India to be prospectively registered before the enrolment of the first participant and to disclose details of the 20 mandatory items of the WHO ICTRP International Clinical Trial Registry Platform (ICTRP) dataset. |
| Vision | 1. To improve transparency and accountability by encouraging full disclosure<br>2. To improve the internal validity of trials conducted in India by facilitating reporting of details of the method of random sequence generation, concealment of allocation of participants to interventions, and blinding of participants, investigators and outcome assessors.<br>3. To conform to accepted ethical standards by disclosing contact details of ethics committee (s) granting approval and providing approval document(s).<br>4. To facilitate reporting of all relevant results of all clinical trials in India and the region by working with the WHO ICTRP |

will not permit opportunities for transparency and facilitation of ethical oversight. National registers with a regional remit, as the CTRI was designed to evolve into, can be especially important in resource-poor settings where individual countries do not have the necessary resources to establish national registers. Such registers will serve the needs of a number of neighbouring countries usually with similar disease burdens. Through sharing technical and operational resources, costs to individual countries will be reduced and promotion of registration could be stream-lined across countries (30).

Duplication of clinical trials across registries is not an insurmountable problem. Two types of duplicate trial registration can happen: unintentional duplication can occur when a trial is registered more than once on the same or different registers and arises due to poor understanding of who is responsible for registering the trial (30). This can be minimized by clear instructions to trial sponsors and investigators or by registering clinical trials through a central agency such as an ethics committee, as is practiced in some countries. Registries are also expected to check for duplicate publications and this can be facilitated by electronic means. Intentional duplication occurs when specific national requirements compel trial sponsors or investigators of multinational trials to register each country's register. Intentional duplicate registration may also occur when different versions of the same trial are conducted in different parts of the world or different jurisdictions, and the country-specific parts of the trial require separate registration (30).

Intentional duplication can be identified by disclosure of the registration identifier of the primary register, in addition to other identifiers, in subsequent registries. A trial may then be identified as a duplicate across registries. The CTRI also endorsed the adoption of the Universal Trial Reference Number (UTRN), proposed by the WHO ICTRP, as a means to detect intentional duplicate registration by providing each trial with a single unique identifying number regardless of where the trial is registered. A pilot study of the utility of the UTRN as a solution to duplicate trial registration is planned by the WHO ICTRP and the results should provide information on the utility of this potential solution.

### *The data elements in the CTRI*

As a Primary Register of the WHO ICTRP, the CTRI is expected to, and does, require as mandatory, full disclosure at the time of registration of the WHO ICTRP and ICMJE 20 item data-set (6). There are additional items required by the CTRI, some of which are mandatory if trial registration is to proceed to completion.

While the WHO ICTRP recognizes that prospective registration of clinical trials is an ethical and scientific imperative, the current 20-item dataset does not include disclosure of ethics committee approval. In fact, the original item 11 titled *Research Ethics Review* was replaced by *Countries of Recruitment* as this was thought to provide more relevant information and because ethics review was considered already mandatory for clinical trials. While this may be true for clinical trials done in many parts of the world, the same cannot be assumed for all clinical trials done in India (31). One of the mandatory CTRI-specific data elements 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 letters, when available (Table 2). 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 a pre-requisite for registration in the hope that mandatory disclosure of the specific ethics committee that cleared the trial as well as proof of this approval may

**Table 2** Data elements specific to the Clinical Trial Registry-India (CTRI)

| Item | Rationale |
|---|---|
| Principal investigator or overall trial coordinator (multi-centre study) name and contact details | To improve transparency and accountability |
| Site/s of study | To improve transparency and accountability and to identify sites where trials are being conducted in order to facilitate ethical oversight |
| Name of ethics committee and approval status[†] | To improve transparency and accountability and to facilitate ethical oversight |
| Regulatory clearance obtained from the Drug Controller General of India[†] | Regulatory requirement; will improve transparency and accountability and facilitate ethical oversight |
| Brief summary | To improve transparency |
| Method of generating randomization sequence | To reduce risk of bias in trial design and improve transparency |
| Method of allocation concealment | To reduce risk of bias in trial design and improve transparency |
| Blinding and masking | To reduce risk of bias in trial design and improve transparency |
| Phase of trial[†] | To improve transparency |
| Estimated duration of trial | To improve transparency |

[†]Mandatory CTRI items required for registration to proceed to completion

lead to more responsible conduct and supervision of the trial (29,31).

Notwithstanding the attention that industry-sponsored trials receive, it is less often appreciated that numerous clinical trials of drugs, psychological interventions, devices and surgery are done every year in medical colleges often with insufficient ethical oversight or even valid research designs (24). These trials are often not reported once the requirements of theses submissions or conference attendance is fulfilled. Those that do make it to publication often reveal important deficiencies in reporting requirements that are likely to have been the result of poor trial design, and journal editorial policy and peer review do not necessarily prevent these trials of doubtful validity from achieving the perceived sanctity of published truth (32).

Attempts to comply with CONSORT requirements (even if mandated by editorial policy of 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 unethical even if the trials are prospectively registered. In an attempt to use prospective trial registration to drive better design and reporting of clinical trials conducted in India, the CTRI data set includes three items pertaining to internal validity that do not form part of the 20-item WHO ICTRP Registration Data Set. Registrants are requested (but not mandated, as yet) to describe the method used for generation of the random sequence, method used to conceal allocation to interventions, and who will be blinded to interventions (Table 2). 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 their trial's results (29–33).

### *The process of registering trials in the CTRI*

Registrants create a login name and password by completing a form when they attempt to register a trial. On receipt of a password confirmation note by email, the registrant can use the chosen username and password to upload the required information on the trial that is being proposed. Once the data is submitted, the CTRI staff checks the submitted information for completeness and whether informative entries have been provided. If needed, the registrant is contacted with any queries. Further, the CTRI staff will verify that the trial is being conducted through contact with Ethics Committees and requisite documents (Table 2) will be verified. Once queries, if any, are clarified, the trial is registered and allocated a unique CTRI registration number. Both the date of submission and date of registration are recorded. Registrants are required to update information on each trial (including patient accrual, trial and publication status) regularly. Further, all the WHO ICTRP fields need to be filled if the trial is to receive a registration number and fulfill (WHO ICTRP/ICMJE) requirements. Incomplete entries are given a provisional registration number that will not suffice for purposes of publication in journals that endorse the ICMJE recommendations for trial registration. The CTRI was designed with the expectation that the UTRN would form the initial process of registration but pending its implementation, this feature has been disabled and a temporary UTRN is automatically generated and assigned by the CTRI software application to any trial that is being processed for submission.

It was hoped that trials which are not verifiable from relevant sources despite attempts to do so by the CTRI staff, but appear complete with respect to the trial information that is provided, are fully registered but marked as "Not verified;" however, this facility has not been implemented as yet. Registration is voluntary and free of cost. The CTRI also provides an audit trial of any amendments to registered entries.

### *Types of trials registered with the CTRI*

The CTRI accepts for registration all clinical intervention trials involving humans that assess health-related outcomes and uses the WHO ICTRP and ICMJE definition of an interventional trial (2,3). While the CTRI is meant primarily to register trials before the enrolment of the first participant, it also accepts for registration trials that are ongoing. It does not, as yet accept retrospective registration of trials that have closed and restricts registration to interventional trials, irrespective of phase of trial or the presence or absence of control groups. It does not register, nor does it intend to register, other types of studies, unlike some other international trials registries.

### *Strategies associated with the launch of the CTRI*

The CTRI was launched on 20 July 2007. Prior to and after the launch, attempts at consensus building have targeted the pharmaceutical industry, academic institutions and medical journal editors.

Medical journal editors, as gatekeepers of scientific publications, were considered an important target. A meeting was held at the ICMR headquarters at New Delhi in October 2007 with the editors of biomedical journals of India to garner their support and commitment to the CTRI and make trial registration a prerequisite for considering a trial for publication in Indian journals. The results of the survey of editorial policy were presented and they were reminded of their editorial responsibilities that include safeguarding the rights of participants, establishing policies of submission, review and acceptance of manuscripts, and working towards improving the quality of the conduct and publication of research (20).

This was followed by a meeting with medical journal editors at the All India Institute of Medical Sciences, New Delhi, organised by the editors of the National Medical Journal of India, and a workshop for editors during the 2nd South Asian Regional Symposium on Evidence-Informed Health Care organized by the South Asian Cochrane Network at the Christian Medical College, Vellore.

In February 2008, the first of a series of editorials appeared endorsing trial registration and signed by the editors of 12 leading Indian medical journals (34–41). These editorials concluded with the statement that, "From January 2010 onwards, we will consider publication of a trial only if it has been registered prospectively if started in or after June 2008; trials undertaken before June 2008 need to be registered retrospectively" (presumably in another publically accessible registry that accepts retrospective registration). Other editorials endorsing trial registration have appeared in scientific journals (42).

### *Governance of the CTRI*

The CTRI is managed by a team based at the National Institute of Medical Statistics, New Delhi that is supported by the ICMR. Funding for the CTRI is from the Department of Science and Technology, the Indian Council of Medical Research and the World Health Organization- India Country Office.

### *Progress with trial registration in the CTRI*

Even though the CTRI was launched in July 2007, technical difficulties delayed the commencement of registration. The first trial was registered on 29 August 2007. Trial registration was initially slow and by 31 March 2008 only 29 trials had been fully registered (33). However, by 10 January 2009, 155 trials had been registered of which 144 trials met the registry's requirements and were assigned full registration numbers, while 11 were assigned temporary or provisional registration numbers. Of the 144 fully registered trials, 12 (7.7%) were registered in 2007, 137 (88.4%) in 2008 and 6 (3.9%) in the first 10 days of 2009. Of these 144, 110 were registered with no additional primary registry's identifier, while 40 (25.8%) also had identifiers for clinicaltrials.gov (www.ct.gov); 2 (1.3%) were additionally registered in the European registry, and 3 (1.9%) carried identifiers for the Australian and New Zealand registry (www.anzctr.org.au). Of the 144 trials, 74 (51.4%) were funded by the pharmaceutical industry, 26 (18.1%) were funded by institutions, 32 (22.2%) were funded by research organizations or governmental agencies and the remainder reported no funding sources. One trial was to be conducted in Nepal.

**Table 3** Compliance with the WHO ICTRP 20 item data set in 144 trials registered in the Clinical Trial Registry- India (CTRI)

| WHO ICTRP item | Disclosed (%) |
|---|---|
| Unique trial number | 144 (100) |
| Trial registration date | 144 (100) |
| Secondary Ids | 144 (100) |
| Funding source(s) | 142 (98.6) |
| Primary sponsor | 100 (100) |
| Secondary sponsor(s) | 100 (100) |
| Contact for primary queries | 143 (99.3) |
| Contact for scientific queries | 143 (99.3) |
| Public title of the study | 144 (100) |
| Scientific title of the study | 144 (100) |
| Countries of recruitment | 144 (100) |
| Health condition(s) or problem(s) studied | 144 (100) |
| Intervention(s) | 139 (96.5) |
| Key inclusion and exclusion criteria | 144 (100) |
| Study type | 144 (100) |
| Anticipated trial start date | 144 (100) |
| Target sample size | 137 (95.1) |
| Recruitment status | 144 (100) |
| Primary outcome(s) | 126 (87.5) |
| Key secondary outcomes | 132 (91.7) |

**Table 4** Compliance with Clinical Trial Registry- India (CTRI) Specific data-set items in 144 trials registered

| CTRI Item | Disclosed (%) |
|---|---|
| Principal investigator or overall trial coordinator (multi-centre study) name and contact details | 114 (79.2) |
| Site(s) of study | 142 (98.6) |
| Name of ethics committee and approval status | 144 (100) |
| Regulatory clearance obtained from the Drug Controller General of India | 144 (100) |
| Brief summary | 135 (93.8) |
| Method of generating randomization sequence | 119 (82.6) |
| Method of allocation concealment | 110 (76.4) |
| Blinding and masking | 122 (84.7) |
| Phase of trial | 143 (99.3) |
| Estimated duration of trial | 137 (88.4) |

Table 3 reports the proportion of trials that were compliant with the WHO ICTRP 20 item data set. Reporting was judged adequate in all registered trials for 13 items. The lowest level of compliance was with disclosing primary and secondary outcomes, which was largely due to inadequate disclosure of time points for assessing these outcomes.

Table 4 details compliance in the 144 registered trials with the CTRI specific data elements. Compliance was over 75% for the three items pertaining to validity (random sequence generation 83%; allocation concealment 76%; blinding 85%), even though these items were not mandatory fields. Compliance with disclosure of ethics approval and regulatory clearances was 100%, but these are mandatory if registration is to proceed to completion.

## Discussion

The CTRI was designed to conform to international requirements of transparency and accountability as well as to cater to local requirements of improving trial design and safeguarding participants' interests. The statement by medical journal editors endorsing trial registration strengthens the CTRI's mandate for disclosure of critical elements of trial protocols and the increasing numbers of trials being fully registered augers well for the future. Compliance of the registered trials on the CTRI with the WHO ICTRP minimum dataset is comparable with trials registered in clinicaltrials.gov for most fields and even better for some, (43). However many challenges remain if all trials conducted in India are to be registered in the CTRI.

### *Challenges facing the CTRI*

The trials currently in the CTRI are likely to represent only a small fraction of ongoing clinical trials in India. For example, a search on clinicaltrials.gov using the term 'India' for trials registered in the US registry but with one or more sites in India yields more than 700 entries. Many of these entries do provide contact details of the Indian investigators or their trial sites. In 2007 alone, 493 trials were registered with the US Food and Drug Administration with sites in India (44). Much remains to be done if all these trials are to be registered on the CTRI so that trial participants are to benefit from the advantages that registration in the CTRI has to offer.

### *Strategies to increase trial registration in the CTRI*

Concerted and widespread efforts are required to encourage prospective registration by all concerned, since registration is currently voluntary. Education and ongoing dialogue are important components of this and the importance of prospective registration and details of registration requirements need to be incorporated into teaching programmes and research methodology courses. Dialogue with drug companies and contract research organisations in India have commenced and should continue to allay unwarranted anxieties. Dialogue with medical editors not committed to trial registration should continue until all Indian Journals follow the lead of the ICMJE and increasing numbers of editors are committing themselves to this international initiative. Consumer groups need to be enlisted to educate potential trial participants on the potential hazards of participating in trials that are not registered in an approved registry. Academic institutions and ethics committees ought to consider clinical trial registration an important part of their mandate for balancing the harms and benefits to the participant. Some have already accepted this mandate and have increased the quality of design of trial protocols in the process (29,33). The CTRI, by requiring ethics committee contact details and approval documents, will complement the bioethics initiative of the Indian Council of Medical Research (ICMR) to identify and eventually accredit all ethics committees in India.

### *Legislation for trial registration in India*

Periodic audits of information disclosed in the CTRI, combined with comparisons of trials approved by the DCGI and independent audits by agencies such as the ICMR of ongoing trials in institutions would further help assess the acceptance of trial registration by the research community (32).

Forging links between ethics committees, regulatory authorities, medical journal editors and clinical trial registries will promote communication among bodies involved in regulation of clinical trials and increase the efficiency of clinical trial registration and facilitate the oversight processes. However, if these fail, the example of legislation, exemplified by the Food and Drug Administration Revitalization Act, provides additional hope (45).

It is not widely appreciated that a *de facto* legislation could soon exist in India that mandates prospective trial registration, even if the formal bills continue to languish in parliament. Schedule Y of the Drugs and Cosmetics Act (16) requires researchers to abide by the World Medical Association's (WMA) Declaration of Helsinki, and the ICMR's ethical guidelines for research. At the recommendation of the WHO-ICTRP, the WMA amended clause 19 of the Declaration to make prospective registration in a publicly accessible register before recruitment of the first subject explicit in the October 2008 amendment of the Declaration of Helsinki. Prospective trial registration is not an explicit requirement in the ICMR guidelines as yet. The ICMR ethical guidelines (15) will also shortly be revised to include endorsement of prospective registration of all trials conducted in India in the CTRI. Since Schedule Y requires researchers to abide by the ICMR guidelines and the Declaration of Helsinki, regulators and ethics committees would then be obliged to support trial registration as a legal as well as an ethical requirement (29).

### *Evidence and health care decisions*

If healthcare decisions in India are to be informed by all the available (and reliable) evidence (47), then concerted action involving all relevant stakeholders, in cooperation with the WHO ICTRP, is crucial to achieve the mission and vision of the CTRI. However, the true success of the CTRI will become apparent only when the results of clinical trials done in India (and the region) are published in easily accessible sources. International efforts to drive the reporting of clinical trials will inform the efforts of the CTRI in this regard. While most medical journals in India that publish clinical trials are available online, many are not indexed in major databases that are commonly searched. Locating these non-indexed

journals is time consuming and finding the relevant clinical trials provides additional difficulties. Authors of systematic reviews and developers of treatment guidelines may not be easily able to locate these trials and their exclusion from consideration and inclusion in the evidence base creates the possibility of biased and unreliable results and findings and conclusions that may not be applicable to health care in the region.

The Indian Medlars Centre (www.indmed.nic.in) is a bibliographic database of Indian biomedical journals maintained by the National Informatics Centre and the ICMR, and MedInd (www.medind.nic.in) provides a one point resource of searchable full text contents of 38 peer reviewed Indian biomedical journals. The South Asian Database of Controlled Clinical Trials (SADCCT; www.cochrane-sadcct.org) contains information about interventional clinical trials in countries in South Asia that have been completed (or are in progress but have interim or follow up results). The SADCCT is restricted to only providing limited information about controlled clinical trials and their sources, not about other types of research, but includes many more journals and sources of trials than the Indian Medlars Centre and covers countries in South Asia other than India. All trials in the SADCCT will be uploaded to the Cochrane Collaboration's Central Register of Controlled Trials (CENTRAL) that forms part of The Cochrane Library (www.thecochranelibrary.com). The SADCCT will provide complementary regional efforts to those of the CTRI and the WHO-ICTRP, and The Cochrane Collaboration (www.cochrane.org), in ensuring that that all the evidence from clinical trials are made publically available to inform evidence-based practice and health care in India and the region.

## Acknowledgements

The author acknowledges the contributions of the CTRI and its leadership in the design, launch and implementation of the CTRI. The author is closely associated with the activities of the WHO-ICTRP, the CTRI and the Cochrane Collaboration and has received travel support from each of these organizations. The author has also received grant support from the WHO ICTRP-India country office, the ICMR, and the Department for International Development (DFID), UK, through the Liverpool School of Tropical Medicine. He has also received travel and grant support from the UK National Health Service via the Universities of Leeds and Nottingham. The views expressed in this paper are those of the author and not necessarily those of any of the aforementioned agencies.

### References

1. World Health Organization. International Clinical Trial Registry Platform (ICTRP). About Registries. [home page on the internet]. World Health Organization, Geneva [cited 10 January 2009]. Available at http://www.who.int/ictrp/network/primary/en/index.html
2. DeAngelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: A statement from the International Committee of Medical Journal Editors. *N Engl J Med* 2004; 351: 1250–51.
3. De Angelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors. *Lancet* 2005; 365: 1827–29.
4. Evans T, Gulmezoglu M, Pang T. Registering clinical trials: An essential role for WHO ICTRP. *Lancet* 2004; 363: 1413–14.
5. World Health Organization. International Clinical Trial Registry Platform (ICTRP). WHO ICTRP Registry Criteria. [home page on the internet]. World Health Organization, Geneva [cited 10 January 2009]. Available at http://www.who.int/ictrp/network/criteria/en/index.html
6. World Health Organization. International Clinical Trial Registry Platform (ICTRP). About Registries. WHO ICTRP Trial Registration Data Set [home page on the internet]. World Health Organization, Geneva [cited 10 January 2009]. Available at http://www.who.int/ictrp/network/trds/en/index.html
7. World Bank. *India. New directions in health sector development at the state level: an operational perspective.* World Bank Report. No. 15753-IN. Population and Human Resources Division, South Asia Country Department II: The World Bank, 1997.
8. van Doorslaer E, O'Donnell O, Rannan-Eliya RP, Somanathan A, Adhikari SR, Garg CC, et al. Effect of payments for health care on poverty estimates in 11 countries in Asia: an analysis of household survey data. *Lancet* 2006; 368: 1357–64.
9. van Doorslaer E, O'Donnell O, Rannan-Eliya RP, Somanathan A, Adhikari SR, Garg CC, et al. Catastrophic payments for health care in Asia. *Health Econ* 2007; 16: 1159–84.
10. Confederation of Indian Industries. National Committee on Healthcare. *CII McKinsey Report*. New Delhi: Confederation of Indian Industries, 2002.
11. National Rural Health Mission. All India Summary of NRHM Programme. [home page on the internet]. Ministry of Health and Family Welfare. Government of India. [cited 10 January, 2009] Available at: http://mohfw.nic.in/NRHM/Documents/Executive_summery_august.pdf
12. Mudur G. India launches national rural health mission. *BMJ* 2005; 330: 920.
13. Jesani A. Medical ethics and patients' rights. *Indian J Social Work* 1993; 54: 173–88.
14. Nundy S, Gulati CM. A new colonialism? – Conducting clinical trials in India. *New Engl J Med* 2005; 352: 1633–36.
15. Indian Council of Medical Research. *Ethical guidelines for biomedical research on human participants*. New Delhi: Indian Council of Medical Research, 2006.
16. Ministry of Health and Family Welfare. Drugs and Cosmetics Act and Rules. [home page on the internet] Central Drugs Standard Control Organization. New Delhi; 2005. [Cited

January 10, 2009] Available from: http://www.cdsco.nic.in/html/Copy%20of%201.%20D&CAct121.pdf
17. Central Drugs Standards Control Organization. *The Drugs and Cosmetics (Amendment) Bill, 2007: Bill No. LVII of 2007. A Bill further to amend the Drugs and Cosmetics Act, 1940*. New Delhi: Central Drugs Standards Control Organization, 2007.
18. Tharyan P. Whose trial is it anyway? Reflections on morality, double standards, uncertainty and criticism in international collaborative health research. *Monash Bioeth Rev* 2006; 25: 53–68.
19. Gulhati CM. Needed: closer scrutiny of clinical trials. *Indian J Med Ethics* 2004; 1: 4–5.
20. WAME syllabus for prospective and newly appointed editors. [Home page on the internet]. World Association of Medical Editors. [cited 10 January 2009]. Available from: http://www.wame.org/resources/editor-s-syllabus
21. CONSORT: Transparent reporting of clinical trials. [home page on the internet]. The CONSORT Group. [updated 8 August 2007; cited 10 January 2009]. Available from: http://www.consort-statement.org/
22. International Committee of Medical Journal Editors (ICMJE). Uniform requirements for manuscripts submitted to biomedical journals. [home page on the internet]. International Committee of Medical Journal Editors (ICMJE). [updated October 2008; cited 10 January 2009]. Available from: http://www.icmje.org
23. Tharyan P, Premkumar TS, Mathew V, Barnabas JP, Manuelraj. Editorial policy and the reporting of randomized controlled trials: survey of instructions to authors and assessment of quality of randomised controlled trials in Indian Medical Journals (2004–2005). *Natl Med J India* 2008; 21: 62–68.
24. Gitanjali B. ICMJE statement on compulsory clinical trial registration: Should Indian journals follow suit? *Indian J Pharmacol* 2005; 37: 207–9.
25. Mudur G. Indian study sparks debate on the use of placebo in psychiatry trials. *BMJ* 2006; 332: 566.
26. Patel V. Ethics of placebo-controlled trial in severe mania. *Indian J Med Ethics* 2006; 3: 11–12.
27. Tharyan P. Placebo-controlled trials in psychiatry on trial. *Indian J Med Ethics* 2006; 3: 13–16.
28. Zarin DA, Ide NC, Tse T, Harlan WR, West JC, Lindberg DA. Issues in the registration of clinical trials. *JAMA* 2007; 297: 2112–20.
29. Tharyan P. Ethics committees and clinical trial registration in India: opportunities, obligations, challenges and solutions. *Indian J Med Ethics* 2007; 4: 168–69.
30. Grobler L, Siegfried N, Askie L, Hooft L, Tharyan P, Antes G. Are national and multinational prospective trial registers necessary? *The Lancet* 2008; 372: 1201–02.
31. Tharyan P. The WHO ICTRP International Clinical Trial Registry Platform and the Indian Clinical Trials Register. *Natl Med J India* 2006; 19: 161–64.
32. Tharyan P. Clinical Trial Registration in India: no longer a dream. *Trop Gasteroenterol* 2008; 29: 1–3.
33. Pandey A, Aggarwal AR, Seth SD, Maulik M, Bano R, Juneja A. Clinical Trial Registry – India: Redefining the conduct of clinical trials. *Indian J Cancer* 2008; 45: 79–82.
34. Satyanarayana K, Sharma A, Parikh P, Vijayan VK, Sahu DK, Nayak BK, Gulati RK, Parikh MN, Singh PP, Bavdekar SB, Sreehari U, Sahni P. Statement on publishing clinical trials in Indian biomedical journals. *Indian J Med Res* 2008; 127: 104–5.
35. Satyanarayana K, Sharma A, Parikh P, Vijayan VK, Sahu DK, Nayak BK, Gulati RK, Parikh MN, Singh PP, Bavdekar SB, Sreehari U, Sahni P. Statement on publishing clinical trials in Indian biomedical journals. *Indian J Ophthalmol* 2008; 56: 177–8.
36. Satyanarayana K, Sharma A, Parikh P, Vijayan VK, Sahu DK, Nayak BK, Gulati RK, Parikh MN, Singh PP, Bavdekar SB, Sreehari U, Sahni P. Statement on publishing clinical trials in Indian biomedical journals. *Indian J Med Sci* 2008; 6: 132–3.
37. Satyanarayana K, Sharma A, Parikh P, Vijayan VK, Sahu DK, Nayak BK, Gulati RK, Parikh MN, Singh PP, Bavdekar SB, Sreehari U, Sahni P. Statement on publishing clinical trials in Indian biomedical journals. *J Postgrad Med* 2008; 54: 78–9.
38. Satyanarayana K, Sharma A, Parikh P, Vijayan VK, Sahu DK, Nayak BK, Gulati RK, Parikh MN, Singh PP, Bavdekar SB, Sreehari U, Sahni P. Statement on publishing clinical trials in Indian biomedical journals. *J Vector Borne Dis.* 2008; 45: 81–2.
39. Satyanarayana K, Sharma A, Parikh P, Vijayan VK, Sahu DK, Nayak BK, Gulati RK, Parikh MN, Singh PP, Bavdekar SB, Sreehari U, Sahni P. Statement on publishing clinical trials in Indian biomedical journals. *Indian J Cancer* 2008; 45: 39–40.
40. Satyanarayana K, Sharma A, Parikh P, Vijayan VK, Sahu DK, Nayak BK, Gulati RK, Parikh MN, Singh PP, Bavdekar SB, Sreehari U, Sahni P. Statement on publishing clinical trials in Indian biomedical journals. *Indian J Pediatr* 2008; 75: 755.
41. Satyanarayana K, Sharma A, Parikh P, Vijayan VK, Sahu DK, Nayak BK, Gulati RK, Parikh MN, Singh PP, Bavdekar SB, Sreehari U, Sahni P. Statement on publishing clinical trials in Indian biomedical journals. *Natl Med J India* 2008; 21: 105–6.
42. Bhatt A. Registration of clinical trials: An idea whose time has come! *Indian J Pharmacol* 2008; 40: 47–8.
43. Zarin DA, Tse T, Ide NC. Trial Registration at ClinicalTrials.gov between May and October 2005. *N Engl J Med* 2005; 353: 2779–87.
44. Normille D. The promise and pitfalls of clinical trials overseas. *Science* 2008; 332: 214–16.
45. Drazen JM, Morrissey S, Curfman GD. Open clinical trials. *N Engl J Med* 2007; 357: 1756–57.
46. World Medical Association. Ethical Principles for Medical Research Involving Human Subjects. [updated 22 October 2008; cited 10 January 2008]. Available from: http://www.wma.net/e/policy/b3.htm
47. Duley L, Tharyan P. O registro de ensaios clínicos como garantia do uso das evidências científicas nas decisões sobre cuidados de saúde [Ensuring health care decisions are informed by all of the evidence: the role of trial registration]. *Cad Saúde Pública* 2008; 24: 2732–33.