Clinical trials registered in clinical trial registry of India: A survey

Sir,

Clinical trials are considered as gold standard in the field of evidence-based medicine. It is observed in various surveys done for Indian and Western journals that there are some problems associated with the reporting of clinical trials, and the quality of reporting of clinical trials is less than satisfactory.[1]

One of the important problems associated with the reporting of clinical trial is "selective reporting" of various methodological aspects. It is also observed that some pharmaceutical companies are involved in unethical conduct of clinical trials.[2] As a direct consequence of these issues, there has been a growing call for accountability and accessibility and transparency of clinical trials in order to reestablish public trust in clinical trial data. This can be done by registering clinical trials in centralized clinical trial registry.[3] For the same objectives, The Clinical Trials Registry—India (CTRI) was launched at the Indian Council of Medical Research's National Institute of Medical Statistics (NIMS) on July 20, 2009.

As this is just the initiation of accumulating data related to clinical trials taking place in India, exploration of this data may give some insight of the situation and some suggestions for improvement like in a survey of clinical trial registries of western countries it was observed that few ethical aspects like assent from minors and post-trial obligations were not reported adequately.[4] Post-trial obligations describe a duty by research sponsors to provide a successfully tested drug to research participants who took part in the relevant clinical trials after the trial has been conducted. The strong need for this was felt to avoid exploitation of participants and to increase trust development in researcher participant relationship. It has been realized that "informed consent" has only limited direct application in pediatrics. Only patients who have appropriate decisional capacity and legal empowerment can give their informed consent to medical care. In all other situations, parents or other surrogates provide informed permission for diagnosis and treatment of children with the assent of child whenever appropriate. Hence, this study was planned with the objective of exploration of clinical trial registry of India for reporting of various parameters such as methodological, ethical considerations, and disease burden to get insight of the present situation.

This study was done at the Department of Pharmacology, Government Medical College, Surat (Gujarat) between February 2010 and May 2010. A team of four reviewers (P.Y., J.K., M.C., and D.S.) evaluated the clinical trials registered in clinical trial registry of India (www.ctri.in). All parameters were collected in predesigned proforma which was based on clinical trial standard data set that contains 29 items. Indian clinical trial registry has nine items extra than World Health Organization recommendations which contains 20 items. All clinical trials registered up to December 2009 were considered for this study.

Table 1: Disease burden in India and clinical trials registered in clinical trial registry of India

Disease	Disease burden in India %	Clinical trials (%)
Infectious diseases including maternal and perinatal infections and diarroheal diseases	50.3	8.99
CVS	10	8.07
CNS	8.5	4.4
Cancer	3.4	18.34
Respiratory conditions	1.5	5.87
Eye diseases	1.4	2.01
Diabetes	0.7	6.42

Only few important diseases are mentioned. On the basis of National Commission on Macroeconomics and Health: Report of the National Commission on Macroeconomics and Health. New Delhi: Ministry of Health and Family Welfare, Government of India; 2005

Table 2: Various parameters of clinical trial registered in clinical trial registry of India

Parameter	All trials (*n*=588)* (%)
Intervention	
a. Drug/allopathic	514 (87.41)
b. Surgery or procedure	17 (2.89)
c. Ayurvedic/herbal	21 (3.57)
d. Counseling or lifestyle interventions	36 (6.12)
Top five speciality are*	
a. Diabetes mellitus	59 (10.03)
b. Cardiovascular diseases	34 (5.78)
c. Bronchial asthma	19 (3.23)
d. COPD	12 (2.04)
e. AIDS	8 (1.36)
No. of trial sites	
a. Single site	191 (32.48)
b. 2–5 sites	152 (25.85)
c. >5–20 sites	219 (37.24)
d. >20	23 (3.91)
e. Not mentioned	3 (0.51)
Sample size	
a. Mentioned	520 (88.43)
b. Not mentioned	68 (11.56)
Outcomes	
a. Only primary	28 (4.76)
b. Primary and secondary both	555 (94.38)
c. Not mentioned	5 (0.85)
Randomization	
a. Randomized	477 (81.12)
b. Not applicable	111 (18.87)
Method of random sequence generation	
a. Computer generated	251 (52.62)
b. Stratified randomization	31 (6.49)
c. Stratified block randomization	25 (5.24)
d. Permuted block randomization	16 (3.35)
Variable	
e. Permuted block randomization	36 (7.54)
Fixed	
f. Coin toss, lottery, random number	7 (1.46)
g. Adaptive	3 (0.62)
h. Random number table	25 (5.24)
i. Pharmacy controlled	1 (0.2)
j. Not mentioned	82 (17.19)
Allocation concealment	
1. Done	384 (65.3)
2. Not applicable	153 (26.02)
3. Not mentioned	51 (8.67)
Method of allocation concealment	
a. Centralized	183 (47.65)
b. Sequentially numbered sealed envelop	74 (19.27)
c. Prenumbered/coded identical	53 (13.8)
Container	
d. Pharmacy controlled	17 (4.42)
e. On site computer	8 (2.08)
f. Open list of random number	20 (5.20)
g. Alternation	1 (0.26)
h. Case record	3 (0.78)
i. Other	25 (6.51)
Blinding	
a. Done	331 (56.29)
b. Not applicable	257 (43.71)
Method of blinding	
a. Open label	250 (42.51)
b. Single blind	45 (7.65)
c. Double blind	275 (46.76)
d. Triple blind	2 (0.34)
e. Not mentioned	9 (1.53)
Phase of trial	
a. Not mentioned	5 (0.85)
b. Not applicable	46 (7.82)
c. Phase 1	31 (5.27)
d. Phase 2	116 (19.72)
e. Phase 3	253 (43.02)
f. Phase 4	74 (12.58)
Combined phase	
a. Phase 1/2	20 (3.4)
b. Phase 2/3	33 (5.61)
c. Phase 3/4	10 (1.7)
Compared by	
a. Placebo	221 (37.5)
b. Active control	158 (26.87)
c. Both	8 (1.36)
d. Not applicable	201 (34.18)
Sponsor	
a. Govt. or semi-govt. organization	107 (18.19)
b. Pharmaceutical companies	438 (74.49)
c. Not mentioned	43 (7.31)
Regulatory approval from DCGI	
a. Obtained	404 (68.7)
b. Awaited	8 (1.36)
c. Not applicable	176 (29.93)
Recruitment	
a. Complete	139 (23.63)
b. Open to recruitment	369 (62.75)
c. Nor yet started	70 (11.9)
d. Suspended	1 (0.17)
e. Terminated	9 (1.53)
Status of trial	
a. Completed	79 (13.43)
b. Still going on	499 (84.86)
c. Suspended	1 (0.17)
d. Terminated	9 (1.53)
Informed consent	
a. Obtained	397 (67.51)
b. Not mentioned	191 (32.48)
c. Assent in case of children from child	None

*Only top five specialties are taken

All parameters are reported as frequency and percentages. Differences between the categorical variables were analyzed by Fisher's exact (two-tailed) test.

It was observed that there is a discrepancy in disease burden of India and areas of clinical trials registered in clinical trial registry of India, particularly in case of infectious diseases that are very common in India, but clinical trials addressing this issue are very less [Table 1]. Surrogate end points were used in 522 (95.7%) clinical trials. Out of these 522 clinical trials mentioning surrogate end points, 201 (38.5%) used more than one surrogate end point in single clinical trial. The use of surrogate end point is significantly more in pharmaceutical company-sponsored clinical trials when compared with clinical trials sponsored by government and autonomous institutions. (97.2% vs 89.7%, P=0.003, Fisher's exact test (two-tailed). Informed consent was mentioned in 67.5% clinical trials. Assent taken from children was not mentioned in any clinical trial although 51 (8.6%) clinical trials were related to childhood diseases. Information regarding availability of drugs to patients after completion of clinical trial (post-trial obligations) was not mentioned in any clinical trial registered in clinical trial registry of India. Sample size was not mentioned in 68 trials. In 31 trials, sample size was less than 25 per group. The median sample size was 120 per group. In 60 trials, the duration of trial was not mentioned. The median duration of the trial was 600 days. Other results related to various parameters are given in Table 2.

Issue of mismatch in global burden of disease and clinical trials published in journals is explored in some studies. In a study done by Paula A *et al*., global burden of disease was compared with the clinical trials published in some leading international journals, and it was observed that many of the important global diseases are not much explored in clinical trials and many published clinical trials have very less international health relevance.[5] In our study for clinical trial registered in clinical trial registry of India, same phenomenon was observed. It has been highlighted that developing countries like India are becoming favorite place for doing the clinical trials because of various factors such as availability of treatment naive patients for various diseases, low cost, availability of large pool of healthcare workers, and availability of specialist hospitals.[6] As this study reveals, majority of clinical trials in India are sponsored by multinational pharmaceutical companies and it can be understood that these companies are doing these trials in India because of various favorable factors mentioned earlier.[6] Hence, it cannot be expected from them to explore those areas which are deficient in Indian healthcare system (infectious diseases and neglected tropical diseases) as it may not suit their economical goal. It is observed that disease to be explored in clinical trials by pharmaceutical companies is not based on healthcare need of that region but based on expected commercial gain. So because of increase in number of clinical trials in India, there is definite economical gain but healthcare need of the country should not be overlooked.[7]

Clinical trials registered in CTRI are not required to submit information regarding post-trial obligations. Declaration of Helsinki (2000 version) instructed sponsors of clinical trials to provide best proven therapy to subjects who were the part of clinical trials after its completion.[8]

Majority of clinical trials registered in CTRI were measuring surrogate end points, and this was significantly more in clinical trials sponsored by pharmaceutical companies. In a study done by Cohen E *et al*., it was observed that clinical trials conducted in developing countries measure surrogate outcomes more when compared with developed countries.[4]

Reporting of assent from children was not mentioned in any clinical trial as it is not required during fulfilling of information. Assent should be taken from children having age more than 7 years before recruiting them in clinical trials.[9] The study done by Cohen E *et al*. observed the same.[4]

We want to appeal administrators of clinical trial registry of India to extend the requirement related to ethics while submitting various parameters in clinical trial registry particularly information related to assent and post-trial obligations.

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