Original Article

Compliance of Mumbai-based clinical trial sites with the quality council of India guidelines and evaluation of the challenges faced by the investigators

Brinal Figer, Nithya Jaideep Gogtay, Urmila Mukund Thatte

Department of Clinical Pharmacology Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India

Abstract

Purpose: A committee chaired by Dr. Ranjit Roy Chaudhary suggested accreditation of investigators, sites and ethics committees to improve the quality of trial conduct in the country. Prior to accreditation, understanding the challenges faced at the sites by investigators could help define the extent of the problem and identify potential solutions. Hence, we conducted the present study.

Methods: Institutional Ethics Committee approval and written informed consent was obtained prior to enrolment. A checklist and a questionnaire was used to assess compliance to Quality Council of India (QCI) standards and the challenges faced by the sites and investigators respectively. Mumbai based investigators listed in the Clinical Trial Registry of India (CTRI) were enrolled. The responses obtained were analysed descriptively. The responses to each question in the checklist were calculated as a proportion and response to each item in the questionnaire was calculated in frequency and percent frequency. All the analysis was done using Microsoft Excel version 2013.

Results: A total of 30 investigators from 69 clinical trial sites agreed to participate. We found that over 80% of the sites complied with standards recommended by the QCI guideline. The most frequently reported issues at the site were lack of space for archival (25%), no System to evaluate adequacy of training (31.81%) and lack of understanding of the technical language of the informed consent form (39.02%).

Conclusion: There is a need of coordinated effort between all the stakeholders to improve the clinical trial conduct at the site.

Keywords: Accreditation, clinical trial site, investigators, Quality Council of India

Address for correspondence: Dr. Urmila Mukund Thatte, Department of Clinical Pharmacology Seth GS Medical College and KEM Hospital, Parel, Mumbai, Maharashtra, India.
E-mail: urmilathatte@gmail.com
Received: 28-01-20, **Revised:** 25-03-20, **Accepted:** 08-04-20, **Published:** 15-01-21.

INTRODUCTION

In July 2013, a committee chaired by Dr. Ranjit Roy Chaudhury developed recommendations to help formulate policies for the approval of drugs, clinical trials, and banning of drugs. This committee suggested that the accreditation of investigators, sites, and ethics committees should be performed to improve the quality of clinical trial conduct in the country.[1] The Ministry of Health and Family Welfare, in response, assigned the job of accreditation of Ethics committees, Clinical Trial Sites and Investigators to

Access this article online	
Quick Response Code:	Website: www.picronline.org
	DOI: 10.4103/picr.PICR_22_20

How to cite this article: Figer B, Gogtay NJ, Thatte UM. Compliance of Mumbai-based clinical trial sites with the Quality Council of India guidelines and evaluation of the challenges faced by the investigators. Perspect Clin Res 2021;12:133-9.

the Quality Council of India (QCI). The QCI-a statutory body under the aegis of the National Accreditation Board for Hospitals and Healthcare providers (NABH) has laid down the minimum essential criteria for accreditation in 2013.[2] Until the time of allocating the task of accreditation of the site to QCI, there were no guidelines regarding the minimum essential requirements for the sites in the country to conduct clinical trials with sponsors selecting sites/investigators based on previous experience and/or information available in the Clinical Trials Registry of India.

As multiple factors contribute to the success of any clinical trial,[3] understanding challenges faced at sites by investigators will help understand the extent of the problem and identify potential solutions. This formed the objective of the present study.

METHODS

Ethics, study design

The cross-sectional study was approved by the Institutional Ethics Committee (EC/0A-131/15), and the participants gave written informed consent.

Study duration and study site

The study was conducted between June 2016 and October 2017 in Mumbai.

Study instruments

A checklist (binary responses only) and a questionnaire (multiple choice answers with free text options) were used. The former was used to assess compliance to QCI standards while the latter was used to assess the challenges faced by the investigator.

Development of the study instruments: Checklist:

1. The checklist was developed by the authors based on the QCI recommendations (http://www.cdsco.nic.in/writereaddata/finalAccreditation%20Standards.pdf).[1] The following themes were addressed-site management, qualifications, experience and training of the staff, site SOPs and documentation practices, protection of participant rights, safety and well-being, clinical trial material, oversight and inputs received during the key informant interview with four clinical research professionals
2. Questionnaire: Clinical Research experts with at least 10 years' experience were approached to identify the themes/issues for the questionnaire content development. The views expressed by the experts were written down by a study team member and these were subsequently analyzed by a qualitative research expert (who also had more than 10 years' experience). The following themes related to clinical trial issues emerged and were built into the questionnaire: Space, equipment, staff (infrastructure), training, protection of clinical research participants, standard operating procedures (SOPs), study documentation and storage, serious adverse event (SAE) related issues, ethics committee-related issue, issues related to funds and sponsor-related issues. Based on these themes, a study instrument comprising of 23 items was developed
3. Validity and Reliability assessment of the questionnaire: This was assessed for content validity by eight subject experts, and the content validity ratio (CVR) calculated.[4] Items with a CVR above 0.5 were retained. Reliability assessment was done using test-retest reliability and the internal consistency and measured using Cronbach's alpha (preset at 0.7).[5]

Postvalidation, a 40-item checklist, and a 25-item questionnaire were developed.

Study sample

All the Mumbai based Clinical trial investigators listed in the Clinical Trial Registry of India for regulatory clinical trials till December 2016 and who consented to participate formed the study sample.

Study procedure

A study team member interviewed investigators who gave consent and administered the checklist and questionnaire to them.

Outcome measures

1. The proportion of sites compliant with the QCI recommendations
2. The most frequent challenges faced by investigators during clinical trial conduct.

Statistical analysis

Descriptive statistics was used. The responses to each question in the checklist were analyzed, and the compliance was calculated as a proportion. As the number of respondents varied for each question, and answers were descriptive in nature, the percent frequency was calculated as given below:

Percentage frequency = (Frequency/total responses) × 100.

For example: For space-related issues, "lack of space for archival" was found to be the most frequent issue reported by 19 sites and a total of 26 investigators have answered the question, the percent frequency was calculated as $19/26 \times 100 = 73.07\%$

The compliance was rated by us-, 60% - average, 60%–75% - Good, 75% and above - Very Good.

All the analysis was done using Microsoft Excel version 2013 (Publisher: Microsoft Corporation, Redmund, Washington, USA, 2016).

RESULTS

Demographics

A total of $n = 69$ clinical trial sites with 97 investigators were identified. twenty three (75.3%) out of 30 of them had at least 10 years and/or conducted at least five regulatory studies. A total of sixteen (53%) were from public hospitals/institutes while 14 (47%) were from private hospitals/institutes. A total of 12 (40%) were male investigators whereas 18 (60%) were female investigators. Most investigators (28/30, 93.33%) were from clinical medicine specialties, whereas only 02/30 (6.66%) were from para clinical specialties.

Responses to the checklist

A total of 25/30 (83.33%) investigators had adequate space and equipment, 24/30 (70%) had adequate staff., 21/30 had their own SOPs, and regularly conducted educational and training programs for the staff. All sites said they used recently approved version of the ICD, while over 50% (16/30) stated that they informed participants about the risks and benefits in the study during the consent process. The measures taken to ensure protection of participants are summarized in Figure 1.

A majority (21/30, 70%) of the study participants were recruited by sites from the outpatient department [Figure 2], and more than 80% of the sites had a safety management plan for the participants. Most sites (14/30, 46.67%) said they reported SAEs within 24 h [Figure 3]. The responses to the some of the major subitems in the checklist are summarized in Table 1.

Response to the questionnaire

The clinical trial sites were riddled with several administrative issues in addition to site facilities and infrastructure. Most frequent among these were the lack of timely approvals for studies from IEC (20.68%) and lack of pharmacist at the trial sites (44.11%) and lack of speakers to conduct training sessions for the staff (11.36%). Many sites stated that they could not verify the adequacy of their training (31.81%). Several concerns pertaining to communication with the sponsor were also observed. These were, constant pressure from the sponsor for recruitment (23.52%), and many were of the opinion that CRAs were not appropriately trained (26.47%). The issues pertaining to infrastructure, ethics, and site facilities were common across the majority

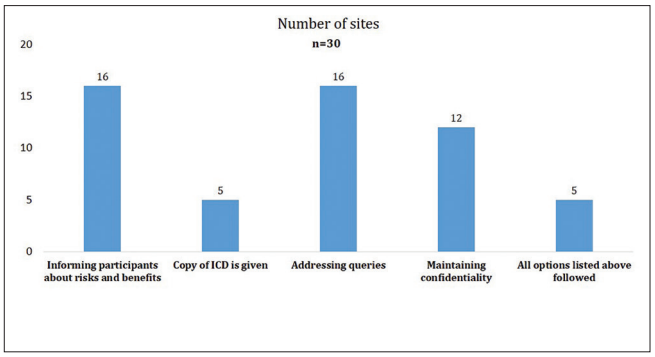

Figure 1: Measures taken at the site for the protection of research participants

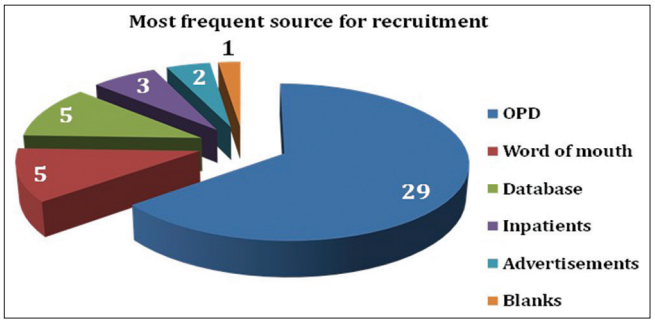

Figure 2: Source of recruitment of participants

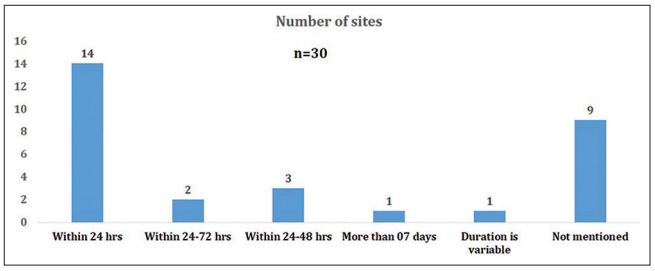

Figure 3: Duration of reporting of serious adverse events seen at the site

of the sites and are summarized in Table 2. Majority of the investigators (n=14) reported SAEs within 24 hours however, at some sites the duration was variable Figure 3.

DISCUSSION

Our study assessed compliance of trial sites (including Investigators/staff) with QCI recommendations and found that most sites showed good compliance with the recommendations.

Give that 80% of sites complied in terms of infrastructure (space, equipment, and staff), it is likely that this has been built by the investigator with help from the pharmaceutical industry and institution over a period given that the city is a hub for regulatory research. The lack of archival space is reflective of the city where space crunch is a known challenge. The

Table 1: Response to the checklist of some major sub items

	n	Compliance	
		yes (n,%)	No (n,%)
Checklist sub item			
Do you have space to conduct clinical trials at your site?	30	25 (83)	5 (16.7)
Diagnostic facilities for clinical trial patients	30	28 (93)	2 (6.7)
Equipments for routine medical assessments	30	19 (63)	11 (36.7)
Devices for emergency treatment and management of SAEs	30	19 (63)	11 (36.7)
Staff			
Do you have adequate and qualified staff to conduct the research at your site?	30	24 (80)	6 (20)
Do you have staff to monitor and maintain the infrastructure?	30	23 (77)	7 (23.3)
SOPs			
SOPs for all clinical trial procedures	29	21 (70)	7 (23.3)
Training			
Do you conduct educational and training programs at your site?	23	21 (70)	2 (6.7)
Protection of subject rights, well-being and safety			
Do you ensure fair and equitable subject selection at your site?	30	30 (100)	0
Does the safety management plan of your site cover the following?	26	26 (100)	0
Medical management			
Documentation and			
Reporting			
Study participants' informed consent process			
Do you use the most recent version of ICDs?	30	30 (100)	NA
Are all the informed consent documented at your site?	30	30 (100)	NA
Do you ensure the adequacy of the informed consent process by taking the following measures?	30	30 (100)	NA
Documenting the informed consent			
Giving participants an opportunity to ask questions			
Giving participants an opportunity to ask questions			
Do you document consent withdrawals and refusals at your site?	30	27 (90)	3 (10)
Safety reporting and management			
How many SAEs have you reported in the last 5 years?	30	Less than five - 9 (30) More than five - 7 (23.3) More than ten - 3 (10) No SAE - 8 (26.7) Not mentioned - 3 (10)	NA
How many of the SAEs were death?	30	Less than two - 5 (16.7) More than two - 2 (6.7) None - 3 (10) Not mentioned/Blanks - 20 (66.66)	
Do you have provisions for medical care and follow up in *cdcase* of SAE at your site?	21	21 (100)	
Clinical trial documentation			
Are the clinical trial records at your site accurate, complete and legible?	30	30 (100)	NA
How do you ensure the accuracy and credibility of the data?	30	30 (100)	NA
Is there the following provision at your site in case of accidental loss or destruction of the data?	27	24 (80)	3 (10)

NA=Not available, SAEs=Serious adverse events, SOPs=Standard operating procedures, ICDs=Informed consent document

high attrition rates may be related to the past downturn as well as inadequate remuneration in academia relative to the pharmaceutical industry and an ill-defined career path. As staff is an important aspect in the capacity building[6,7] at the site, defining career paths and adequate remuneration at hospitals/Institutions and creation of clinical research secretariats would help retain them in academia.

SOPs remain a key challenge with inadequate updation and lack of training. The main reasons for nonconduct of training stated were nonavailability of time and lack of experts/faculty for training. Most of the sites were tertiary referral hospitals/centers attached to medical colleges with investigators handling several studies at the same time along with routine patient care. Administrative difficulties such as nonavailability of funds and timely approvals for the study, as seen for the study, were also key issues. Introduction in the academia of "dedicated/protected research time" could be a possible solution.

The delayed reporting of the SAEs to the site by the participants/relatives was another issue that has been now addressed by the sixth amendment to the drugs and cosmetics rules which states that "*the investigator should report all SAEs to the drug regulatory body of India (DCGI), sponsor of the trial, and the concerned EC that approved the trial protocol within 24 h of occurrence of the SAE.*"[8]

Many investigators and sites did not have a database of participants and faced difficulties during recruitment.

Table 2: Key challenges faced by the investigator

Themes	Participants who responded (*n*)	Issues	Frequency of occurrence (%)
Infrastructure-space	29	Archival	10 (25)
		Obtaining consent	9 (22.5)
		Participant follow ups	7 (17.5)
		Medical care and treatment	5 (12.5)
		Document storage	7 (17.5)
		Drug storage all issues	101 (2.52.5)
Equipments	24	Laboratory procedures are not validated	5 (20.83)
		No system for regular maintenance and calibration	4 (16.66)
		No refrigerator and deep freezer for IP storage	4 (16.66)
		No diagnostic laboratory	3 (12.5)
		No equipment at site	3 (12.5)
		No issues	5 (20.83)
Staff	25	Staff shortage	12 (25)
		Less experienced staff	13 (27.08)
		High attrition and turn over	14 (29.16)
		Impossible to get MBBS staff	1 (2.08)
		No coordination between staff	3 (6.25)
		No issues	5 (10.41)
SOPs	25	Beach of SOPs	3 (9.67)
		SOPs are not updated	5 (16.12)
		Staff trained only during violations	8 (25.80)
		There are typographical errors	1 (3.22)
		No specific SOPs and therefore ethics committee SOPs are used	1 (3.22)
		SOPs do not cover all activities	4 (12.90)
		No issues	9 (29.03)
Safety management	22	No intensivist in the team	4 (18.18)
		SAEs are reported late	4 (18.18)
		Lack of consensus between investigators, sponsors and ethics committees	1 (4.54)
		No issues	13 (59.09)
Informed consent process	25	Participants do not understand technical language	16 (39.02)
		Difficulty to convince LARs	4 (9.75)
		Lack of autonomy	13 (31.70)
		Participants are not comfortable with AV consent	5 (12.19)
		No issues	3 (7.31)
Recruitment related issues	29	No database	12 (25.53)
		High consent refusal	5 (10.63)
		Not enough eligible participants	8 (17.02)
		High migrant population	6 (12.76)
		No issues	16 (34.04)
		Training sessions are not conducted periodically	12 (27.27)
		No expert speakers	5 (11.36)
		No issues	5 (11.36)
Fair and equitable selection	28	Poor literacy and therapeutic misconception	11 (27.5)
		Reliance of physician	12 (30)
		Constant pressure from sponsor	10 (25)
		Participants are well educated and wary about research	5 (12.5)
		No issues	2 (5)
		No SOPs for adverse event reporting	1 (3.44)
		No issues	18 (62.06)
Informed consent documentation	23	No documentation of photocopy of ICD given	9 (36)
		More time required for informed consent	1 (4)
		Wrong version of the informed consent is signed	5 (20)
		No issues	10 (40)
Clinical trial documentation	30	Study documents are incompletely filled	6 (27.27)
		Loss of original documents	1 (4.54)
		Documents are as hard copies with no back up	1 (4.54)
		No internal monitoring	7 (31.81)
		No provision of data retrieval	7 (31.81)

SAEs=Serious adverse events, SOPs=Standard operating procedures, ICD=Informed consent document, IP=Investigational product, AV=Audio visual, LARs=Legally acceptable representative

In regulatory studies, in addition to these difficulties, investigators mentioned that the recruitment procedure is made difficult by the "technical language" of the Informed Consent forms. This makes recruitment of participants especially those with poor literacy challenging.[9-11] A study conducted by Michael Pascha *et al*. recommended that the informed consent must have the readability of 4th grade to ensure that participants understand it and autonomy is maintained[12] and use of lucid language for drafting the ICDs should be encouraged. There is a need for investigators to work with the pharmaceutical industry to develop consent forms that are comprehensible. The ethics committees also play a key role here. However, complex study protocols (oncology, for example) in multinational studies could still prove to be a challenge.[13-15]

We found that investigators stated an increased reliance on physician by the participants to take decision regarding participation. Our observation is similar to a study conducted by Doshi *et al*., where the majority of the patient participants stated that the reason for participation was because "*my doctor asked me to*."[16] Another important operational issue highlighted was the "lack of a dedicated pharmacist at the site." A pharmacist apart from investigational product management can play a crucial role in convincing the participants about adherence to the protocol and medication compliance during trials. We also found issues such as nondocumentation of the photocopy of the ICD to the patients, lack of data backup, and internal monitoring which could compromise the quality of documentation and data integrity. Previously published Inspection and audit findings have often cited documentation deficiencies[17] and adequate steps must be taken to address them.

The study is limited by the fact that no physical verification of the sites was done, the study time frame was short and the systems were only assessed through the checklist and questionnaire. Also, the study observations are restricted to only Mumbai and other regions/cities of the country were not studied. The study has been carried over a limited period of over 2 years (2016 and 2017), and the data generated through this research represents the scenario of that time.

In summary, the investigator has numerous responsibilities during the conduct of clinical trials and is on the "frontline" while ensuring that the rights, safety, and well-being of study participants are protected. However, the discharge of these responsibilities requires a coordinated effort between all the stakeholders, including sponsors, to further improve clinical trial conduct.

CONCLUSION

The existing systems at the sites are in compliance with the QCI recommendations however, there are several deficiencies within these systems which could be addressed by developing site-specific guidelines. Such an initiative could be taken at the institute level.

Acknowledgments

We are grateful to Dr V Singh for the assistance in analysis for the qualitative data. We are also grateful to all the participants in the study for taking time out and filling the questionnaire. Thanks are also due to the Dean, Seth GS Medical College and KEM Hospital for giving the facilities to carry out the work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Report of the Prof.Ranjit oy Chaudhury Expert Committee to Formulate Policy and Guidelines for Approval of New Drugs, Clinical Trials and Banning of Drugs. Available from: http://www.cdsco.nic.in/writereaddata/Report_of_Dr_Ranjit_Roy.pdf. [Last accessed on 2019 Dec 02].
2. National Accreditation Board for Hospitals and Healthcare Providers (NABH). Accreditation Standards for Clinical Trials in India.: Available from: http://www.cdsco.nic.in/writereaddata/finalAccreditation%20Standards.pdf. [Last accessed on 2019 Dec 02].
3. Pereira P. Quality in Clinical research activities. Role of instituition/clinical trial site. J. Nat Accred Board Hosp Healthcare Providers 2015;2:4-8.
4. Ayre C, Scally A. Critical values for Lawshe's content validity ratio: Revisiting the original methods of calculation. Meas Eval Couns Develop 2014;47:79-86.
5. Tavakol M, Dennick R. Making sense of Cronbach's alpha. Int J Med Educ 2011;2:53-5.
6. Thatte UM, Bavdekar SB. Clinical research in India: Great expectations? J Postgrad Med 2008;54:318-23.
7. Investigator Meetings (IM) in Clinical Trial. Available from: http://www.jli.edu.in/blog/investigator-meeting-im-in-clinical-trials/. [Last accessed on 2020 Apr 02].
8. Drugs and Cosmetics (Sixth Amendment) Rules, 2014 (DCR- 6th Adm – English and Hindi/Hindī). (Effective Date: June 12, 2015) Department of Health, Ministry of Health and Family Welfare, Government of India; 12 December, 2014. Available from: http://www.cdsco.nic.in/writereaddata/Notificatiohn%20on%20Compensation%20on%20clincial%20trial%20 (1).pdf. [Last accessed on 18 Jan 2019].
9. The Gazette of India, New Delhi: Ministry of Health and Family Welfare. Notification 12th December, 2014; G.S.R. 889(E). Available from: http://www.cdsco.nic.in/writereaddata/Notificatiohn%20on%20Compensation%20on%20clincial%20trial%20(1).pdf. [Last accessed on 2020 Mar 06].
10. Fredman SJ, Baucom DH, Gremore TM, Castellani AM, Kallman TA, Porter LS, *et al*. Quantifying the recruitment challenges with couple-based interventions for cancer: Applications to early-stage breast cancer. Psychooncology 2009;18:667-73.

11. Kern SE. Challenges in conducting clinical trials in children: Approaches for improving performance. Expert Rev Clin Pharmacol 2009;2:609-17.
12. Frank G. Current challenges in clinical trial patient recruitment and enrollment. SOCRA Source. 2004:30-8. [Google Scholar].
13. Kadam RA, Borde SU, Madas SA, Salvi SS, Limaye SS. Challenges in recruitment and retention of clinical trial subjects. Perspect Clin Res 2016;7:137-43.
14. Paasche-Orlow MK, Taylor HA, Brancati FL. Readability standards for informed-consent forms as compared with actual readability. N Engl J Med 2003;348:721-6.
15. Doshi MS, Kulkarni SP, Ghia CJ, Gogtay NJ, Thatte UM. Evaluation of factors that motivate participants to consent for non-therapeutic trials in India. J Med Ethics 2013;39:391-6.
16. Fogel DB. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. Contemp Clin Trials Commun 2018;11:156-64.
17. Marwah R, Van de Voorde K, Parchman J. Good clinical practice regulatory inspections: Lessons for Indian investigator sites. Perspect Clin Res 2010;1:151-5.