

ETHICS OF ETHICS COMMITTEES

Protection of human research participants: accreditation of programmes in the Indian context

NEELAMBARI BHOSALE, SHAGOOFA NIGAR, SOMA DAS, UMA DIVATE, PATHIK DIVATE

Jehangir Clinical Development Centre, Jehangir Hospital Premises, 32, Sassoon Road, Pune 411 001, Maharashtra INDIA Author for correspondence: Neelambari Bhosale
e-mail: neelambari@jcdc.co.in

Abstract

The recent negative media reports on the status of participants in clinical trials in India, together with the concerns expressed by the regulatory bodies, have raised questions regarding India's credibility in the conduct of clinical research. Even though the regulations require the registration of trials with the Clinical Trial Registry – India and despite the recently mandated registration of ethics committees (ECs) with the Drugs Controller General of India, the lack of governmental audit and accreditation procedures and bodies has resulted in inadequate protection of human participants in clinical research. Institutions and research sites would benefit by implementing a human research protection programme, which would safeguard the rights, safety and well-being of participants in clinical trials, in addition to improving the processes and procedures for the conduct of the trial. The Jehangir Clinical Development Centre, Pune has received accreditation from the Association for the Accreditation of Human Research Protection Programme (AAHRPP). A unique feature of the AAHRPP is the integrative nature of the programme, wherein the sponsors of the trial, investigators, EC members and institution work towards the common goal of protecting research participants. Here, we discuss the improvement needed in the quality standards of institutions for them to be able to meet the requirements of the AAHRPP. We also suggest the need for a governmental accreditation body, which will be required for the future promotion of and improvement in the standards for clinical practice in India.

Background

In the past two decades, India was a passive participant in most of the research on the development of new drugs, which constitutes a large proportion of the pharmaceutical research taking place (1). However, after signing the World Trade Organisation agreement in 2005 and becoming a party to the Trade-Related Intellectual Property Rights Act (TRIPS), India came on par with global destinations for the conduct of clinical trials. This, along with the availability of a large population of drug-naïve patients, well-trained medical professionals and sophisticated technological infrastructure, has made India an attractive destination for the conduct of global clinical trials (2). The number of trials conducted across the country increased from a paltry 40–50 in 2003 to almost 1850 in 2011 (3). However, as this trend developed, so have concerns regarding the ethical implications of outsourcing clinical trials to developing countries, because of the prevalence of poverty and

illiteracy, as well as the lack of awareness (4,5). The Indian media and regulatory bodies have been reflecting such concerns by stressing issues such as serious adverse events (SAEs), training and functioning of ethics committees (ECs), vulnerable patients, improper procedures for obtaining informed consent, and provision of compensation to participants in case of injury related to clinical trials (6). In such a scenario, it is important for the stakeholders, ie the investigators, institution, EC and sponsors, to take their role in the research seriously, and to understand their responsibility for protecting the participants in the trial. They should try to ensure that the clinical research conducted by them is of the highest quality and meets the highest standards of ethics to safeguard the rights, safety and well-being of the participants. One way of promoting compliance with high standards is to implement a robust and comprehensive human research protection programme (HRPP). The objective of such a programme is that all the stakeholders should work towards ensuring that research is conducted ethically and that the data generated are credible.

Such a programme would include mainly policies, guidelines and written procedures to be followed while conducting and reviewing research involving human subjects. Under an HRPP, the researchers and research staff, EC, sponsors and research participants themselves would adopt a comprehensive and integrated approach towards the protection of human subjects of research. Another advantage of such a programme is that it would ensure research of good quality as the audits and inspections conducted in India are either random audits or for-cause audits by sponsors or regulatory agencies (7). The Drugs Controller General of India (DCGI) has recently laid down the norm that clinical trials should be monitored annually. However, this is still in the process of being implemented across the research sites in India. The DCGI has also mandated the registration of ethics committees with the governing body, in addition to the registration of individual trials with the Clinical Trial Registry – India (CTR-I). Nonetheless, the lack of governmental audit and accreditation procedures may put the credibility of research on human subjects in doubt.

Need for accreditation: beyond quality assurance and quality control

The Jehangir Clinical Development Centre (JCDC), Pune is a clinical research site with rich experience in conducting Phase I to IV clinical trials across various therapeutic areas, including

oncology, haemato-oncology, endocrinology, rheumatoid arthritis and neurology. JCDC was formed in 2006 and has conducted around 170 trials since, which makes it one of the most experienced investigator sites in India. It has a quality management system compliant with ISO 9001:2008 standard requirements in place. In 2012, an inspection of the organisation by the United States Food and Drug Administration (US FDA) in relation to a clinical trial in haematology yielded no deviations.

JCDC decided to go forward with an accreditation programme to improve upon its existing practices in the conduct of research and to demonstrate its ethical standards in the review and conduct of research. Applying for accreditation from the Association for the Accreditation of Human Research Protection Programme (AAHRPP), which is highly regarded, was an obvious choice because of the integrated nature of the programme, wherein the institution, investigators, EC, sponsors and research participants work towards the protection of the participants in research trials.

Organisations conducting research can benefit from accreditation from an internationally recognised body in that this helps them bring their procedures and policies on par with global standards. An organisation which has received accreditation is formally recognised to have the competence to carry out tasks within a specified scope, with the highest possible ethical and professional standards (8). While accreditation is voluntary and variable, it is now accepted worldwide as an important aspect of an organisation's internal activities pertaining to the improvement of quality (9).

Journey to AAHRPP

To begin with, before applying for the accreditation, JCDC needed to have a thorough knowledge of the local regulations as well as the AAHRPP's requirements, which are categorised into three domains: (i) the organisation, (ii) the IRB/EC, and (iii) the researchers and research staff; they are further categorised into standards, which consist of various elements. A dedicated team consisting of key members from different departments of the organisation and EC members was set up to aid JCDC in conducting a gap analysis. The gap analysis was useful in identifying the procedures and areas which were deficient and which needed to be developed in accordance with the AAHRPP's requirements. The organisation then worked diligently on the findings of the analysis.

Following the incorporation of all the changes made to the procedures in accordance with the AAHRPP's guidelines, the Step I application was sent to the AAHRPP's accreditation committee for a review process. The committee determines whether the written documents meet the accreditation standards. After reviewing the Step I application, the committee provided element-level feedback. Once the feedback was addressed and the changes were incorporated into the standard operating procedures (SOPs), a revised application was sent to the AAHRPP committee. After the changes were deemed satisfactory, JCDC submitted the Step II application. Its entire staff, including the EC members, investigators and

research personnel, received training on the revised procedures. These procedures were then implemented. On dates agreed upon mutually, AAHRPP site visitors conducted site visit, during which they made a thorough assessment of the organisation's compliance with AAHRPP standards. The assessment consisted of reviewing the documents and interviewing selected key personnel from the organisation, including the investigators, EC members, and senior management and staff.

The AAHRPP promptly sent a follow-up Draft Site Visit Report to the organisation. JCDC addressed the issues and concerns identified and sent the committee a response, which was then reviewed by the Council on Accreditation. On the basis of its overall preparedness, JCDC was awarded "full accreditation" status.

The primary changes made in the procedures included the following.

Domain I: Organisation

The AAHRPP standards in the domain of "organisation" required amendments to the existing SOPs. JCDC added new policies to its existing body of policies on and procedures for the ethical conduct of trials to ensure the safety of the participants. The organisation developed various tools, forms and checklists to complement the SOPs so as to be able to demonstrate effective implementation of the written procedures. Some examples of the changes made to the procedures are described below:

- The AAHRPP requires that sufficient activities be undertaken to enhance the understanding of human research among participants, prospective participants and their communities. JCDC developed a participant information brochure in the vernacular languages with the objective of educating participants on various aspects of clinical trials and their rights as research participants. The brochure also informed them about the organisation's HRPP, with the aim of helping them take a well-informed decision before participating in a clinical trial.
- For the English-speaking population, the organisation dedicated a section of its website, the "Participant Outreach Corner", to information on the participant's rights. This section also provided links to information on trials at the local and national levels, besides giving the participants a channel to provide their feedback, express their concerns and make complaints. JCDC also developed a policy for obtaining written feedback from research participants. The feedback questionnaires were in the vernacular languages so as to be able to better evaluate the participants' comprehension of informed consent, the quality of care received at the site and the facilities at the site. Policies were framed to facilitate corrective and preventive action in case of any negative feedback.
- The AAHRPP required the existence of a policy on the disclosure of conflict of interest to ensure that the conduct and outcome of trials are not biased by conflicting financial and/or non-financial interests of the investigator, EC

members and key leaders of the organisation. A policy was framed to identify, evaluate, manage and minimise or eliminate JCDC's proprietary interests, financial investments or holdings, as well as the personal financial interests of key leaders of the organisation and investigators when such interests could conflict with the organisation's obligations to protect research participants, maintain the integrity of the research, and ensure the credibility of the human research protection programme.

- In the case of sponsored research, JCDC laid out criteria relating to clinical trial agreements and other funding agreements. Procedures were developed to ensure that not just the financial but also the legal aspects of the contracts, such as medical management in case of research-related injury and the maintenance of confidentiality, are reviewed and evaluated in detail, and are agreed upon by both parties before the submission of the initial application to the EC.
- An internal quality assurance (QA) department, which is an independent unit within JCDC, conducts routine audits and inspections to assess compliance with the protocol, applicable regulations, written SOPs, organisational policy and professional standards. It also identifies the strengths and weaknesses of the programme at the organisation, as well as opportunities to improve its quality, efficiency and effectiveness. Indicators for the measurement of quality were developed as required by the AAHRPP.
- JCDC framed a policy for the reporting of any unanticipated problem or event which might pose a risk to research participants or others, eg members of the research team and the public.
- Procedures were established so that the individuals responsible for oversight of research do not experience undue influence from the organisation or others.

Domain II: Institutional review board or ethics committee

- A comprehensive SOP was developed to incorporate all the requirements of the local regulatory bodies and AAHRPP. The SOPs documented the details of matters such as the composition of the EC, roles and responsibilities of the EC members, quorum requirements, use of consultants, and disclosure of conflict of interest of EC members. They also included systematic review procedures and documentations.
- Tools and checklists were developed and implemented to demonstrate compliance with the SOPs.
- As per the local regulations, continuing review is required for every active trial. As per the AAHRPP's requirements, detailed procedures were laid down for continuing review of research studies to ensure complete review of the status of studies.
- JCDC introduced a procedure whereby the EC's approval of a research study would be valid for only a period of one year.

- Annual performance review of the EC members was commenced so as to bring more credibility to the functioning of the EC.
- Procedures were developed with respect to the disclosure of conflict of interest of the EC members to ensure unbiased and transparent procedures.
- A robust training programme, including training sessions on regulations and the policies and procedures of JCDC, was developed for the members of the EC. They were also provided with a well-defined job description, so that they could discharge their responsibilities in the organisation efficiently.
- An administrative team was given the responsibility of looking after the operational functioning and documentation requirements of the EC.

Domain III: Researcher and research staff

JCDC made sure that all the researchers and research staff were qualified in terms of education, training and experience. Systematic and detailed procedures and processes were introduced for the selection of researchers and research staff. The job descriptions were revised so that appropriate roles and responsibilities could be given to appropriate personnel. The roles and responsibilities of each member of the organisation were laid out more clearly. SOPs were developed on training and education and a training plan was brought out to outline and schedule the initial as well as continuing training programmes for the site personnel. The researchers and staff of the organisation were given adequate and appropriate training on a regular basis, keeping in view their roles within the organisation. Procedures and processes related to the management of clinical trials were developed so as to aid the research staff in carrying out their everyday activities more efficiently.

Completing one year of excellence

With its "full accreditation" status and being one of only three sites in India to be accredited by the AAHRPP, JCDC has gained global recognition. Moreover, preparing for the accreditation process provided JCDC with a much-needed opportunity to reflect upon and improve its existing SOPs in line with the global standards of ethical and good-quality clinical research.

Organisation

The feedback collected from the customers (sponsors, contract research organisations) and patients helped in measuring the satisfaction index, which may aid in improving customer-patient-institution relations. Any complaints are addressed through root-cause analysis and corrective action and preventive action (CAPA) is implemented. Following the accreditation, there was an increase in the confidence shown by the sponsors of clinical trials, viz pharmaceutical companies and CROs. The contracts and other funding agreements for sponsored research studies are evaluated for their financial

clauses, provisions pertaining to arrangements for medical care and research-related injury, as well as to monitoring of research studies, terms regarding confidentiality, etc. prior to the submission of the initial protocol to the EC. The aim is to ensure ethical conduct of research for the protection of the participants. As a part of its ongoing programme for the quality improvement, the organisation carried out a Failure Mode and Effects Analysis (FMEA) to assess the key procedures followed in the conduct of clinical research. The FMEA touched upon the areas of i. informed consent, ii. investigational product management, storage, dispensing and accountability, iii. safety management, iv. site personnel training, v. source documentation and essential documents, vi. patient identification and screening process.

This exercise helped JCDC to identify failure modes which could be avoided with the use of better control measures. In the process, the organisation became a worldwide pilot site for conducting quality improvement activity.

JCDC is implementing an improved QA programme. This includes root-cause analysis of all deviations, which aids in the identification of areas that need improvement. Regular internal audits are conducted at a periodicity which ensures that weak areas are identified in the preliminary stage itself. The scope of the audits includes compliance with the protocol, local regulations, SOPs and EC documentation. Periodic evaluations are carried out to ensure that the members of the research staff are well versed with their job responsibilities, as well as the applicable regulatory requirements. The QA programme also audits the EC documentation, and reviews the EC minutes as well as the facilities available at the site.

Institutional review board or ethics committee

The functioning of the EC has improved considerably following the accreditation process. The accreditation process has played a pivotal role in promoting a holistic review process, which has made it easier to form a considered opinion on any new protocol, as well as to demonstrate JCDC's compliance with the local regulations and written SOPs. In its everyday functioning, the EC employs various tools, such as the initial application form and the form for the disclosure of conflict of interest. A detailed and updated account of the EC's minutes is maintained and the documentation practices have improved considerably, as is evident from the QA audit reports. The accreditation has greatly helped in increasing the efficiency of the EC. It has resulted in a reduction of almost 43% in its timelines (33 days in April 2012 to 19 days in December 2012) for the review of a protocol. The timeline, which is reckoned from the day of the submission of the protocol to its final approval, is one of the quality indicators employed at the organisation. In the past one year, since JCDC received AAHRPP accreditation, 52 protocols have been submitted for initial review, with 51 studies obtaining approval and 1 being deferred for reasons related to its scientific validity. There has also been a marked improvement in the quality of the data collected for monitoring the quality indicators employed at the

organisation. Any reported deviations from the protocol are assessed by the EC to determine whether they are of a serious and continuing nature, and also to determine the correctness of the CAPA implemented. More detailed information is now available to the members of the EC regarding the criteria to be followed while evaluating and reviewing research protocols at the time of the initial application and during subsequent reviews.

Researchers and research staff

The organisation now has a more detailed set of written policies and procedures for implementation, which have helped the research team. Through the process of accreditation, the research personnel at the site have become trained in and aware of the conduct of ethical research, HRPP and other applicable regulatory guidelines. The regular periodic training programmes have become more structured. There is also a greater focus on the improvement of the knowledge and expertise of the investigators, EC members and research staff, who are responsible for protecting the rights and welfare of research participants. Hence, it can be asserted that there has been a marked improvement in the quality of the clinical research conducted by the organisation, as well as in patient-customer relations. This includes the operation of the EC, and the professional development of the researchers and research staff.

Communication

In terms of communication, the EC and JCDC are now well connected due to the use of better communication practices. Prior to the accreditation, the QA team never interacted with the EC. Now, however, reports of all the audits conducted by the QA team are forwarded to the EC to make for greater transparency of procedures.

Discussion

Accreditation evaluates the capability or performance of the organisation as an entity. It is not a one-time process, but requires continued efforts thereafter to improve upon the procedures relating to quality. Preparation for accreditation is not possible without self-assessment and this provides an organisation with an opportunity to determine its compliance with the standards, as well as to identify areas that require improvement (10). The accreditation programmes implemented worldwide are known to improve quality, as well as the safety standards of healthcare organisations. Accredited organisations provide care of a better quality compared to non-accredited organisations (9,11,12). Also, clinical performance has been found to be positively correlated to accreditation (13).

In India, accreditation of clinical research sites and ECs is a voluntary process. Recent amendments in the regulations make it mandatory for ECs and individual trials to be registered with the DCGI and the CTRI, respectively. However, there is no local or governmental accreditation body in place for the authorisation of organisations to carry out research that

keeps the protection of the research participants in mind. Organisations opt for accreditation as a means of improving quality. Accreditation can benefit them by helping them develop a strong HRPP that is at par with the local and global standards. It can also enhance their credibility in a larger range of research activities. Lack of accreditation has led to a wide inconsistency in the way individual ECs work in India. Hence, a governmental accreditation body and an accreditation programme that is well thought out and implemented can possibly establish confidence in India's research capabilities and capacity to ensure that participants in clinical research are given adequate protection.

References

1. Ganju A. Clinical trials in India: should you or should you not participate? [Internet]. Available from: http://www.iscr.org/Resource/126681048_Clinical%20trial%20India.pdf
2. Julka PK. Clinical trials in India: dilemmas for developing countries. *Issues in Clinical Research*. 2007 Apr;69-71.
3. Yee A. Regulation failing to keep up with India's trials boom. *Lancet*. 2012 Feb 4;379(9814):397-8.
4. Bhatt A. Indian clinical trials: paradigm shift from speed to quality? *Perspect Clin Res*. 2012 Jan-Mar;3(1):1-3.
5. Shah JY, Phadtare A, Rajgor D, Vaghasia M, Pradhan S, Zelko H, Pietrobon R. What leads Indians to participate in clinical trials? A meta-analysis of qualitative studies. *PLoS One*. 2010 May 20;5(5):e10730. doi: 10.1371/journal.pone.0010730
6. Jadhav M, Bhatt A. Ethics in clinical research in India: A survey of clinical research professionals' perceptions. *Perspect Clin Res*. 2013 Jan-Mar;4:4-8.
7. Bairy KL, Pereira P. Accreditation of human research protection program: an Indian perspective. *Perspect Clin Res*. 2012 Apr-Jun;3:80-4.
8. Wadhwa V, Rai S, Thukral T, Chopra M. Laboratory quality management system: road to accreditation and beyond. *Indian J Med Microbiol*. 2012 Apr-Jun;30 (2):131-40.
9. Greenfield D, Braithwaite J. Health sector accreditation research: a systematic review. *Int J Qual Health Care*. 2008 June;20 (3):172-83.
10. Sleem H, Abdelhai RA, Al-Abdallat I, Al-Naif M, Gabr HM, Kehil E, Sadiq BB, Yousef R, Elsayed D, Sulaiman S, Silverman H. Development of an accessible self-assessment tool for research ethics committees in developing countries. *J Empir Res Hum Res Ethics*. 2010 Sep;5(3):85-98. doi: 10.1525/jer.2010.5.3.85.
11. Hinchcliff R, Greenfield D, Moldovan M, Pawsey M, Mumford V, Westbrook JI, Braithwaite J. Evaluation of current Australian health service accreditation processes (ACCREDIT-CAP): protocol for a mixed-method research project. *BMJ Open*. 2012;0:e001726. doi:10.1136/bmjopen-2012-001726
12. Greenfield D, Pawsey M, Braithwaite J. What motivates professionals to engage in the accreditation of healthcare organizations? *Int J Qual Health Care*. 2011 Feb;23(1):8-14.
13. Braithwaite J, Greenfield D, Westbrook J, Pawsey M, Westbrook M, Gibberd R, Naylor J, Nathan S, Robinson M, Runciman B, Jackson M, Travaglia J, Johnston B, Yen D, McDonald H, Low L, Redman S, Johnson B, Corbett A, Hennessy D, Clark J, Lancaster J. Health service accreditation as a predictor of clinical and organizational performance: a blinded, random, stratified study. *Qual Saf Health Care*. 2010 Feb;19(1):14-21. doi: 10.1136/qshc.2009.033928

Be a part of *IJME*

IJME invites readers to submit research studies, comments, case studies, reports, reviews, letters, as also poems, short stories, original paintings and photographs of print quality (both in colour and B/W) to be considered for publication.

All submitted matter is subject to peer review.

Contributors are neither paid nor charged any fee for published matter.