Vol 1, Issue 1, 2014

ISSN: 2349-7041

Review Article

REGULATORY AFFAIRS IN CLINICAL RESEARCH: PRESENT SCENARIO

[1]SAMRAT PAUL*, [2]INDRAJIT NATH, [3]FAHAD ZAFAR

[1]Jadavpur University, Department of Pharmaceutical Technology, [2]Jadavpur University, Department of Pharmaceutical Technology, [3]Depertment of Physiology,City College, University of Calcutta

Email: paulsamrat.12@gmail.com

ABSTRACT

Ethical concern on practice of medicine mostly centered around the practice of therapeutic medicine. In biomedical and clinical research both researchers and participants are committed to improve of the health of society. Thus it is essential that research on human beings is governed by core ethical and regulatory principle.

Global clinical research is exploring India. Drug companies are drawn to India for several reason. Government should take necessary step against or for a clinical trial conducting in India. This review article explores mainly present scenario and challenges on clinical research in India.

Keywords: Clinical trial, Bioethics, Indian scenario

INTRODUCTION

Concern about the ethics of practice of medicine has a long history but until the middle of last century, they are mostly centered around the practice of therapeutic medicine, not research medicine. The world health organization recognized a need for guidelines that were broader in scope than the Nuremberg code, and as a result, The Declaration of Helsinki was emerged out as recommendations guideline to medical doctor in biomedical research involving human subjects. This was adopted by the world medical society in 1964.

According to the Belmont report issued on 30 september, 1978 [(1)], three fundamental ethical principles for using any human subject in research are,

1. Respect for persons.
2. Beneficence: The philosophy of " Do no harm"
3. Justice: Ensuring responsible, non exploitative and well considered procedures are administered fairly.

The International conference on Harmonization of technical Requirements for registration of Pharmaceuticals for human use (ICH) is unique to bring together the regulatory authorities and pharmaceutical industries of Europe, Japan and the US to discuss scientific and technical aspect of drug registration.

ICH in its guideline finalized in July 2010 [(2)], include following topics in relevant area. 1. Dose response studies, 2. Ethics factor, 3. Good clinical practice, 4. Clinical Trial. 5. Principle for clinical evaluations by therapeutic category. 6. Clinical evaluation, Pharmacogenomics.

International law of Clinical trial:

There are many international instruments that confer and safeguard the rights of participants in clinical trials. Modern ethics in human research mainly emerged after World War II, when Nazi physicians used prisoners for "inhuman experiments". This resulted in the creation of the Nuremberg code in 1947, which clearly stated voluntary consent as an absolute requirement for human subject research [(3)].

In 1964, the Declaration of Helsinki [(4,5)], proposed by the world medical association changed some of the absolute rules of the Nuremberg code; for example it allowed the use of surrogate consent in the case of individuals with impaired decision making. On European level, the EU has issued its directive on good practice in clinical trials and the council of Europe has issued a convention of human rights and Biomedicine on Biomedical research [(6)]. Most recently UNESCO has developed a Universal declaration on bioethics and human rights [(7)].

International covenant on civil and political rights (ICCPR),1996 seriously focused on human rights in clinical trials. Article 7 of ICCPR is to be read " No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishments. In particular, no one shall be subjected without his free consent to medical or scientific experiementation [(8)].

Clinical research carried out in accordance with general principles would not violate this provision. Recently XVI International AIDS conference in Toronto, UNAIDS presented an ethical argument as to effective treatment. UNAIDS representative considered these issued as ethical and not obligatory legal issues [(9)].

However, The council for International organizations of Medical sciences (CIOMS), revised ethical guideline, 1993 make some reference to the declaration of Helsinki and it is the fundamental document in the field of ethics in biomedical research [(10)].

Recent update in Global pharmacovigilence

Pharmacovigilence systems and processes are undergoing major changes worldwide, especially in Europe Union and USA from 2012 onwords. This will remain a whole new preparation and a whole new approach for pharmaceutical organization including manufacturers and CRO operating in these regions. The changes are fundamental and basic in nature where the whole system is going into an overhaul, including ICSR processing, periodic safety update reports, and the good pharmacovigilence practices [(11)].

Regulation in clinical trial: Indian Scenari

Drug companies are drawn to India for several reason, including largest pool of patient suffering from cancer, diabetes, wide spectrum of diseases, multi-resistant pneumonia etc, Rapid Patient recruitment, Technical competent workforce, low cost and friendly drug-control system and data generated in India is accepted by all major conferences and journals [(11)]. According to Joint study by international consultancy Ernst and young and federation of Indian chamber of commerce and Industry, India now participate in over 7% of all global phase III and 3.2 % of all global Phase II trial [(12)].

Indian regulation: Clinical trial in india are regulated by Schedule Y of Drug and cosmetic rules 1945. The rules were revised in 2005, under the

updated rules, the schedule Y was extensively revised to bring the Indian regulation up to per with internationally accepted definitions and procedure. The rules are enforced by the office of the DCGI [13,14]. The rules are as follows.

1. For new drug being developed in india, clinical trial have to be conducted in india from phase I
2. For marketing approval of drugs already approved in in others countries, a multicentric phase III clinical trial is required to established the drug impact on the Indian ethnic population.
3. An application for new indication of an already approved drug is treated as an application for new drug's approval.
4. New formulation of approved drug may be subjected to bioequivalence study.
5. Phase I trial of foreign drugs were not permitted except for drug of special relevance to India.

All the mentioned regulatory requirements whether National or International law/rule or guidelines are basically having a same target.

1. Respect and protection of Human rights of trial subject.
2. Reasonable compensation of trial subject.
3. Participation of subject with consent.
4. Full scientific, medical and ethical justification to conduct the trial.

The trial sponsor must obtain approval from DCGI before starting a trial. The trial can not be started without clearance from the local ethics review committee at each site [13].

Before 2005, the drug and cosmetic rule suggested, but did not require, that clinical trial documents be reviewed by an ethics review committee. The rules as amended in January 2005 require that the clinical study report include a statement that the trial was conducted according to the principles of the declaration of Helsinki, Indian good clinical practice guidelines, and the Indian Council for Medical Research (ICMR) ethical guidelines for biomedical research on humans [14].

The ICMR first published details guidelines for biomedical research in 2000. These include guidelines for ethical review. Revised guidelines published in 2006 state that the ethics review committee is also responsible for monitoring trials [15].

India's Clinical trial Registry has all the 20 items of the WHO Clinical trial registry platform [16]. In addition, there are items such as :

1. Principle investigator Name and communicating Address.
2. Name of ethics committee and approval status.
3. Regulatory clearance from DCGI
4. Estimate duration of trial and phase of trial
5. Site of study
6. Brief summary
7. Methods of randomization sequences and allocation concealment and blinding and masking.

In recent years India has tried to tighten clinical trial regulations to counter claims poor practices. The next step is equipping regulators to enforce new guidelines. The manpower and infrastructure of CDSCO is being strengthened for strict compliance [17].

The CDSCO is now working with expert bodies to develop guidelines and introduce regulation for the mandatory registration of CRO and Institutional review board and ethics committee [18].

Different regulatory bodies in India (Table 1)

Updating of current regulatory process

The basic Indian statues for governing all aspect of clinical research or trial are 1. Drug and Cosmetic Act 1940. 2. Schedule Y of Drug and Cosmetic Rules 1945 together with all of its appendices. 3. Registration of Clinical trial in ICMR clinical trial registry 4.Clinical trial inspection programme by CDSCO officers [13, 16, 17].

Schedule Y defines the requirement and guidelines for import and manufacture of new drug for sale or for clinical trials [13].

Clinical trial can only be initiated after obtaining written permission from DCGI and IEC. DCGI have already issued Draft guidelines for registration of all clinical research organizations involved clinical trial in India [19,20].

Timeline to clear the files have been notified by DCGI in there website for all application such as clinical trial, BE study, Marketing authorization applications [14].

Daily dispatch section is being uploaded by CDSCO website. Registration of ethics committeein India has already been carried out [21]. DCGI is gearing up to lay down stringent guideline for strict monitoring of clinical trial in the country. Depending on inspection DCGI will be able to withdraw, suspend, or hold back the permission to the trial [16, 17].

Ethics committee and its challenges for clinical research in India:

Ethics implies moral code of conduct defining right and wrong and there by guiding behavior in civil society. Many ethical questions can arise in the practice of medicine and conduct of biomedical research [22]. A research ethics committee is any group formally designated by an institute or body to review, approve the initiation and monitor biomedical research involving human subjects [23].

The composition of EC has to be as per applicable guidelines. In India all institution carry out biomedical research involving human beings are expected to follow revised ICMR Ethical guideline, 2006 [24,25]. This guideline recommended that EC should comprise between 5 – 15 member as follows.

Chairperson (from outside the institution), Member secretary

At least one individual from each of following categories

Basic medical scientist, Clinician, Legal expert, Social scientist/philosopher/priest

and Lay person.

Challenges before ethics committee permission in India: [26]

1. Ethics committee should not be made up exclusively of scientific experts. Some time of risk and benefit may be more easily identified by non scientific member, particularly those from legal, social, or cultural background.
2. Clinical research for academic purpose which have neither commercial sponsor nor large scale funding.
3. Determining the risk benefit balance.
4. Compensation for trial related injury.

CONCLUSION

In biomedical research, both researchers and participants are committed to improve of the health of participant and the society at large. It is thus essential that such research in all its variations is governed by core ethical and regulatory principle.

Global clinical research is exploring India. In the past three years many patients died in trials in India. Many investigations were alleged in violation of clinical trial regulation, warning letters, temporary trial bans, suspension of research licenses were some out come. Inspite of all present pitfalls, the country is certainly gearing up to attract more and more researcher from around the world to conduct there clinical trial studies in India.

The regulatory system is being polished. Single window clearance for application is planned in order to reduce the approval procedure to between two or six weeks. Laws are being amended to facilate the entry of global clinical trial. Massive and concerted efforts are on train research professional and increase the base of investigator and supportive staff. These initiatives are certain to improved the current situation. This will ensure generation of high quality data for international submission.

REFERENCE

1. Jennifer S.A Brief Review of the Belmont Report. Dimensions of Critical Care Nursing. 2010; 29: 173–174.
2. ICH harmonization for better health, Efficacy Guideline.1995 Available at: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html
3. Bulletin of the World Health Organization, Volume 86, Number 8: august 2008, PP 577-656. Available at: http://www.who.int/bulletin/volumes/86/8/en/

4. Tyebkhan G.Declaration of Helsinki: the ethical cornerstone of human clinical research. Indian J. dermatol, venereal, leprol.2003; 69: 245–247
5. Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Available at: http://www.wma.net/ en/30publications/ 10policies/b3/index.html
6. Medicinal products for human use. Available at: http://ec.europa.eu/ health/ human-use/clinical-trials/
7. Cheryl C M, Global bioethics: did the universal declaration on bioethics and human rights miss the boat?. J Med Ethics. 2007; 33: 588–590.
8. International Covenant on Civil and Political Rights. Available at: http://www.ohchr.org/en/professionalinterest/pages/ccpr.aspx
9. AIDS 2006 Evaluation Report - International AIDS Society. Available at: www.iasociety.org/Web/WebContent/File/Old/PDF/1339.pdf
10. International Ethical Guidelines for Biomedical Research - cioms
11. Available at: http://www.cioms.ch/publications/guidelines/guidelines _nov_2002_blurb.htm.
12. Bhatt A. Clinical trial in India: Pangs of globalization. Indian J Pharmacol.2004; 36: 207-208
13. RNCOS, Booming Clinical Trials Market in India, September 2009. Available at: www.rncos.com/Report/IM564.htm
14. Schedule Y *(*ammended version) - CDSCO**. Available at: http://cdsco.nic.in /html/schedule-y%20%28amended%20version-2005%29%20original.htm.**
15. India simplifies clinical trial regulatory process – Outsourcing, Available at:
16. http://www.outsourcing-pharma.com/Clinical-Development/India-simplifies-clinical-trial-regulatory-process
17. ICMR, Ethical guidelines for Biomedical Research on Human participants,2006, Available at: WWW.icmr.nic.in/ethical _guidelines.pdf
18. India makes it mandatory to register clinical trials, RAJ pharma online,22 May.2009.
19. CDSCO, Good Clinical Practice For Clinical Research In India, Schedule Y, Available at: http://cdsco.nic.in/html/GCP1.html
20. CDSCO, Guidence for Industry, Document No CT/71108,Version 1.1 Available at: http://cdsco.nic.in/CDSCO-guidence for industry.pdf
21. Mohammed I et al. Clinical research regulation in India-history, development, initiatives, challenges and controversies: Still long way to go.J Pharm Bioallied Sci. 2013; 5: 2–9
22. Sharma H, Parekh S. Clinical Trials Regulations in India. Pharmaceutical Regulatory Affairs: Open Access 2012
23. Registration of Ethics Committee - Central Drugs Standard Control Organisation. Available at: www.cdsco.nic.in/573(E).pdf
24. Resnik DB. *What is* Ethics in *Research* & Why is it Important?
25. Available from: http://www.niehs.nih.gov/research/resources/bioethics/whatis/
26. 23 William W M. Composition and function of ethical committees. J Med Ethics. 1975; 1: 23–29
27. Research ethics committees: Basic concepts for capasity-building.Geneva: world health organisation,2009. Available from: www.who.int/ethics/ Ethics_basic_concepts_ENG.pdf.
28. biomedical research involving human beings: ICMR Ethical guideline, 2006 Available from: http://www.icmr.nic.in.
29. Srinivasan s, Nikarge S. Ethical concern in Clinical trial in india: an investigation. Mumbai: center for studies in Ethics and Rights,2009. Available from: www.fairdrugs.org/.../**Ethical_concerns_in_clinical_trials_in_India**