

New Clinical Trials Regulations-2013 in India & its Possible Impact on Indian Clinical Trials Framework

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ABSTRACT

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Indian regulators recently enforced two new clinical trials regulations namely "122 DAB- Compensation in case of injury or death during clinical trial" [Drugs & Cosmetics (First Amendment) Rules, 2013] & "122 DAC, (1) Permission to conduct Clinical Trial" [Drugs & Cosmetics (Second Amendment) Rules, 2013] that promise to reform Clinical-Trials conducted in India. Clinical trial sponsors are now liable for injuries or deaths that occur during the course of a clinical trial, and will be required to compensate subjects or the subject's family. The compensation mechanism does appear to be very comprehensive and is very strongly in favor of the volunteer who participate in the trials. The regulations insist on medical management to be provided to the volunteer for as long as required and also indicate that financial compensation should be paid to the volunteers or their nominee. The regulations also define cases which would be termed as clinical trials related injury/death. Product inefficacy has been termed as a clinical trial injury.

This paper views the recent amendments as a whole, & provides a rationale for change, and offers an interrelated set of recommendations to improve the protection of human participants and enable the amendment to operate more efficiently.

Keywords: CDSCO, Clinical trial regulations, DCGI, ethical committee, ICMR.

INTRODUCTION

New Clinical Trials Regulations Issued By ICMR And CDSCO:

Recently on 30 January 2013, & 1 February 2013 the Indian Council of Medical Research (ICMR) and the Central Drugs Standards Control Organization (CDSCO) of the Directorate General of Health Services of the Ministry of Health and Family Welfare issued two new clinical trials regulations namely

- 122 DAB- Compensation in case of injury or death during clinical trial. (Drugs & Cosmetics (First Amendment) Rules, 2013)
- 122 DAC, (1) Permission to conduct Clinical Trial (Drugs & Cosmetics (Second Amendment) Rules, 2013)

In the Drugs and Cosmetics Rules 1945, after rule 122 DAA, "122 DAB- Compensation in case of injury or death during clinical trial" & "122 DAC, (1) Permission to conduct Clinical Trial" rules have been inserted.^{1,2}

These two new enforcements made it mandatory for investigators and sponsors of clinical trial to address issues of serious adverse events such as death of subjects involved in trials and fixing a formula for grant of adequate compensation

in such cases. Though DCGI by introducing new rules for the conduct of drug trials in India, promises to reform future of clinical trials in India, many stakeholders of clinical research sector feel that DCGI is trying to provide simple & quick answers to the concerns which were raised in the Indian Parliament and other forums regarding payment of compensation in the cases of injury or death in clinical trials in India.

"122 DAB- Compensation in case of injury or death during clinical trial." which apply to all forms of clinical research (industry sponsored, funded by government or investigator initiated). Its new provisions are given in Table 1

In the present form amendment called "122 DAC, (1) Permission to conduct Clinical Trial" gives directives, permits the local & central licensing authority to make any changes to a trial protocol regarding the "objective, design, subject population, subject eligibility, assessments, conduct and treatment", "if considered necessary".³

This paper views the recent amendments as a whole & attempt to crystallize problems which can arise due to its implementation & provide some recommendations to improve the protection of human participants in trial and enable the amendment to operate more efficiently.

Problem 1: Research Related Injury & Inherent Risk of Injury in Research.

When a subject is injured as a result of participation in a research study it is called as "research related injury". As per recent amendment, "122 DAB- Compensation in case of

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Table 1: Highlights new provisions of “122 DAB- Compensation in case of injury or death during clinical trial.”

- Clinical trial sponsors are now liable for injuries or deaths that occur during the course of a clinical trial, and will be required to compensate subjects or the subject's family.
- The trial sponsor will have to provide the trial subject with free “medical management” for as long as it would be required.
- Registration of ethics committees and regular monitoring of clinical trials is compulsory.
- Detailed procedures for payment of financial compensation are included.
- It states that any report of serious adverse event (SAE) (SAE of death occurring in clinical trial, after due analysis shall be forwarded by the Sponsor to Chairman of Ethics Committee and Chairman of the Expert Committee constituted by Licensing authority with a copy of the report to the licensing authority and head of the institution where trial has been conducted within ten calendar days of occurrence of SAE of death.
- The compensation guidelines has given Ethics Committees (ECs) duty of determining the degree of risk and then calculating the compensation amount to be paid for research related injuries including death.

injury or death during clinical trial”, any injury or death of the subject occurring in clinical trial due to reasons mentioned in Table 2 shall be considered as clinical trial related injury or death and the subject or his/her nominee(s), as the case may be, are entitled for financial compensation for such injury or death:

The risks of “research related injury” depend on the treatment being studied and the health of the volunteer participating in the trial. Such injuries may range from minor harms (such as

Table 2: Clinical trial related injury according to “122 DAB- Compensation in case of injury or death during clinical trial”

1. Adverse effect of the investigational product(s).
2. Violation of approved protocols, scientific misconduct or negligence by the sponsor or his representative, or the investigator.
3. Failure of investigational product to provide intended therapeutic effect.
4. Use of placebo in placebo controlled trial.
5. Adverse effects due to concomitant medication excluding standard care, necessitated as a part of approved protocol.
6. For injury to child *in-utero* because of participation of parent in clinical trial.
7. Any clinical trial procedures involved in the study.

bruises due to a study procedure or vomiting due to a new drug), to major injuries (such as organ damage or temporary physical disability), to catastrophic injuries (such as permanent disability or death). Injuries can be physical, psychological/emotional, social or economic and may require only acute or emergency care, or long term medical care.⁴

According to US FDA, a clinical trial tests the potential treatments (drug, medical device, or biologic, such as a vaccine, blood product, or gene therapy) in human volunteers to see whether they should be approved for wider use in the general population. It is not known whether the potential medical treatment offers benefit to patients until clinical research on that treatment is complete.⁵ Clinical trials offer no guarantees. On the other hand, especially in oncology trials when standard treatments fail, or none exist, clinical research trials sometimes can offer hope. In short, risk of injury is inherent in any research.⁶ It is often very difficult to separate injuries traceable to the research from those that arise from the underlying disease being studied.

In clinical studies, an adverse event consists of any unfavorable medical occurrence in a subject, whether or not expected. It can be a new or worsening symptom, or disease. It can be caused by the study or be unrelated to the study. Numerous adverse events (Table No.3) are a matter of great concern for human subject's protection and the safety profile of an experimental drug or device.⁷

In the recent amendment, injuries & adverse events (AEs) are not defined and categorized based on the severity, seriousness.

Problem 2: Issue of Mandatory compensation

“122 DAB- Compensation in case of injury or death during clinical trial” makes provision for mandatory compensation for the following

Table 3: Adverse event terminology

1. Adverse event
2. Adverse drug experience
3. Life-threatening adverse event
4. Life-threatening adverse drug experience
5. Life-threatening suspected adverse reaction
6. Serious adverse event
7. Serious adverse drug experience
8. Serious suspected adverse reaction
9. Suspected adverse reaction
10. Unexpected adverse event
11. Unexpected adverse drug experience
12. Unexpected suspected adverse reaction

- Failure of an investigational product to provide intended therapeutic effect.
- Administration of placebo providing no therapeutic benefits.
- Adverse effects due to concomitant medications.

Clinical trials are sets of tests in medical research and drug development that generate safety and efficacy data (or more specifically, information about adverse drug reactions and adverse effects of other treatments) for health interventions (e.g., drugs, diagnostics, devices, therapy protocols).⁸ In an investigational drug, the research may or may not get the desired result. Moreover, during informed consent process, the subjects needs to be informed before enrolling in a new drug trial, that they may not get the intended effect of the drug. Compensating patients being treated with new investigational products because the product did not have its intended therapeutic effect is absurd norm.

Placebo trials are carried out in new drug studies, when there is no existing drug to compare. The placebo is not expected to provide therapeutic benefit. Compensation being provided for patients because the placebo does not have a therapeutic effect is not only absurd but shocking too.

Patients with disease are frequently prescribed multiple drug therapy, most of which are standard or routine treatment which would be given to patients regardless of whether they are research participants or not. In addition, patients take the investigational drug as part of the research protocol. Adverse events occurring due to the other concomitant medications are common and are in no way related to the research itself. Having to compensate for injury resulting from these concomitant medications is again an absurd norm.

Above three points are specifically mentioned in the existing ICMR guidelines as not being entitled to compensation but the CDSCO guidelines made it compulsory.⁹

Phase I trials of investigational agents for cancer are a key step in cancer drug development. The primary objective of a Phase I trial is to determine the maximum tolerated dose (MTD), administration schedule and toxicity profile of an investigational drug and it provides a suitable option for patients who have exhausted available lines of therapy, or for those patients for whom no standard therapy exists. As far as volunteers of clinical trial of cancer are concerned, almost all patients have co-morbidities and cancer-related symptoms that require administration of concomitant medications.^{10,11} Having to compensate for injury resulting from these concomitant medications in phase I trial on cancer patients will have disastrous effect in oncology trials.

Problem 3: Lack of Expertise of Ethics Committees (ECs) & New Challenges

At present EC members see their responsibilities limited to providing approval to research proposals submitted for review as they are ambiguous about their roles and responsibilities Ethics committees face following hurdles.

Lack of trained manpower, administrative support & necessary expertise or experience to determine the exact quantum of compensation or to decide whether fair compensation was paid, Inadequate training, space allocated for EC operations, remuneration offered to members serving on EC boards. In addition to this, there is no proper communication network between the ECs functional in the various parts of the country and the DCGI.

According to the recently introduced amendment, the issue of volunteers being compensated for loss of time/wages in case of an injury has been made mandatory, therefore the DCGI designates the EC as an important regulator of ethical research & placed very important responsibilities of determining compensation on Ethics Committees. Therefore,

- EC members will need specific policy for compensation complying with 122 DAB amendment, ICMR guidelines, Schedule Y, Association of the British Pharmaceutical Industry (ABPI) guidelines & Indian Good Clinical Practices (GCP) guidelines which would be able to make distinctions in instance of medical negligence, fraud or protocol deviations leading to injury of participants. Now it is required to set up mechanism to differentiate protocol deviation related injuries from other adverse events. A tricky situation in case of death of a volunteer during a trial can occur.
- EC members should be trained enough to find out the conditions under which the patient may suffer the injury. Source documentation, protocol compliance, standard of medical care provided to the participants during the trial will have to be looked at in detail by the EC members before they give approval.
- It is most important to make the participant aware of his rights during the trial participation in terms of compensation to avoid further problems.

Problem 4: Assessing Adverse Events

At present Ethical Committee has to deal with different issues of ethics of clinical trials as given in Table 4.¹²

Assessing adverse event reports & reactions can be a major burden for ethics committees and investigators, because of the high volume and ambiguous nature of such events. Currently, FDA regulations for reporting adverse events are complex, and confusing.¹³ The regulations need to be

Table 4: Different issues which ethical committee has to deal with clinical trials

1	Informed consent process
2	Qualification of investigators
3	Vulnerable participants
4	Participant recruitment procedures
5	Conflict of interest and indemnity
6	Risk-benefit balance
7	Privacy and confidentiality
8	Clinical trial registration
9	Data safety monitoring
10	Essential clinical trial documents
11	Clinical trial insurance
12	Dissemination of trial results.

simplified and should be in written format so that investigators, sponsors and ethics committees understand what constitutes an adverse event, type of event to be reported and should define the required communication and co-ordination channels among ethics committees and safety monitoring entities, such as data safety monitoring boards, investigators, sponsors, and regulatory agencies.

Problem 5: DCGI Failed In Implementing Compensation Issues Addressed By Various Existing Indian Clinical Trial Laws

Indian law for clinical trials is based on the Declaration of Helsinki, the ICH-GCP Guidelines & International Ethical Guidelines for Biomedical Research involving human subjects by Council for International Organizations of Medical Sciences (CIOMS). Indian law for clinical trials has mentioned the need for the provision of compensation to participants for research related injuries according to following legislation:

- Schedule Y of 2005 (amended)
- Indian GCP Guidelines for Clinical Trials (Clause 2.4.7)
- The ICMR Ethical Guidelines for Biomedical Research on Human participants, 2000 (Section V in General ethical Issues) and 2006 (in Chapters III and IV)

The publication of the ICMR guidelines (Yr. 2000) & and the Indian GCP guidelines (Yr. 2001) stresses on the importance of informed consent document (ICD). According to the guidelines, volunteers who suffer physical injury as a result of their participation are entitled to financial or other assistance for any temporary/permanent impairment/disability. In case of death, their dependents are entitled to material compensation. Furthermore, applications submitted to Ethics Committees for prospective studies should provide the

proposed financial plan (including, if necessary, insurance) to manage adverse events and compensation for trial related injuries.

In spite of these provisions, regulators never raised any issues regarding compensation, even though several clinical trials have been approved by the DCGI, over the last 5 years.¹⁴

DCGI & ICMR: Work in Isolation.

SOP's for EC are formulated by collaborative efforts of the ICMR & Forum for Ethics Review Committees of Asia Pacific (FERCAP) & the revised version of Schedule Y, released by DCGI describes the roles and responsibilities of EC members & provides clarity on the regulatory responsibilities of EC functions. Both the ICMR, and DCGI, do not have any autonomy over the research reviewed and approved by the ECs in our country. The ICMR guidelines are not legislated, hence, the ECs cannot act against those who violate the prescribed guidelines. Thus, the role of the EC is merely restricted to being an advisory to research.

Problem 6: Insurance Related Documents

In present scenario, clinical research sponsors either apply for the product liability or clinical trial specific annual contracts with insurance agencies. In the case of multinational studies, sponsors generally prefer a global insurance cover or combination of global Master Policy plus individual local policies on a per trial/per country basis. This ensures that the client has the benefit of a harmonized and consistent insurance program. In the current system, only sponsors are generally more aware about the contracts & only insurance certificates issued by insurance providers is given along with most of the documents submitted to ECs. As a result of this, investigators and EC members are always unaware of the details of the contracts.

- At present, the insurance cover offered only to compensate a volunteer in case of any additional complications that may arise due to participation in a trial. All insurance policies very clearly exclude coverage for claims where the test drug/product fails to perform its intended purpose. Insurance companies are not contemplating deletion of this exclusion in light of the recent regulatory changes. This would have a direct impact on the sponsors/CROs and they would incur a higher financial burden. This could also lead to international sponsors not showing any more interest in the Indian Territory to conduct their clinical trials.
- Indian insurance sector should formulate insurance plan which have a rapid response and fast turnaround to coverage requests & also pays for many of the routine medical costs for participants in approved clinical trials.
- No clinical research program is the same as another. Each

client's needs should be specifically reflected in the coverage offered.

- "No fault compensation" should be offered
- Local policies should be provided in local languages.

As per amendment 122 DAC,(1) Permission to conduct Clinical Trial (Drugs & Cosmetics (Second Amendment) Rules,2013) the local authority may, "if considered necessary," impose additional conditions regarding the "objective, design, subject population, subject eligibility, assessments, conduct and treatment of" a proposed clinical trial.³

State Food and Drugs Administration (FDA), the agency for enforcing the Food, Drug and Cosmetic Act in the state, is taking initiatives to strictly implement D&C Act and Food Safety and Standards Act (FSSA) Act in the state. If local authority mentioned in the above amendment is state FDA then on one hand it would be an additional burden imposed on under-staff state FDA and on other hand CRO will have to tackle one more bureaucratic hurdle at local level.

DISCUSSION

Clinical trials industry in India is going through the regulatory evolution phase. The Government recently notified new rules for the conduct of drug trials in India, making it mandatory for investigators and sponsors to address issues of serious adverse events such as death of subjects involved in trials and fixing a formula for grant of adequate compensation in such cases. This 'protectionist proactive' approach adopted by India is very strongly in favor of the volunteers who participate in the trials. This has caused drastic fall in clinical trials this year. Not only have the number of trial approvals in the country reduced, there has also been a significant reduction in the number of sponsoring pharmaceutical firms applying for such approvals. Trials could move out to cost comparable countries such as Malaysia and Thailand. India would lose its advantage of its own assets like large and easy-to-access population with much lower cost than in the developed world. In the last few years clinical research industry was struggling and now it would be more tough.

With stringent norms & law, drug regulatory bodies can ask questions, conduct an inquiry, and take action. Apart from that, stringent norms & law will not guarantee appropriate care and compensation. Unless India introduces a more multifaceted and interconnected system of protections, appropriate care and compensation would be far beyond the means of the researchers, their sponsors, and their institutions. Present amendment has not yet taken cognizance of issues related to the varying compensation amounts in international and national trials. Fear of compensation may hamper academic initiative in areas with no perceived

marketability or economic gain. With new stringent norms, Indian drug regulators may add another set of regulatory bottle-necks which has to be resolved, as trials are reducing.

It is necessary to have a regulatory system which will ensure the welfare of a volunteer; however, there is also an urgent need to safeguard the industry from collapsing all of a sudden. Keeping the regulations in line with international standards/jurisdictions would be prudent to make it a win-win situation to all. Without this, it is quite possible that the clinical trial industry in India would not grow, it may actually see a de-growth which would definitely hurt the country's economy itself.

Present amendment focuses largely on compensation issues rather than identifying and implementing the acceptable conditions for exposure of some individuals to risks and burdens for the benefit of society at large.¹⁵

By focusing on protocol review, subject recruitment practices, informed consent procedures & adverse event monitoring, clinical research can be carried out. By adapting universal principles of justice in principles of Indian clinical trial laws, the effective participation of oppressed population in decision-making can only promote ethical side of an Indian clinical research in Indian setting. In clinical research, as such every stakeholder should consider research participants as central players, who should be protected from any harm for which an existing norms & laws have given enough emphasis on research ethics.¹⁶

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