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Impact of Regulatory Amendment on Human Subjects, Clinical Research Industries and its stakeholder in India.

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Abstract

India is one of the major destinations for conducting clinical trials. The Drug Controller General of India (DCGI) is the governing body responsible for all pharmaceutical-research and regulatory issues in India. While conducting clinical trials in India, regulations have come to ensure safety and well-being of the study subjects in the trial.

But, it has seen due to unethical Clinical Trials, Subject's rights were compromised and unprotected. This is one of the main reasons for the clinical research amendment and make regulation subject friendly by protecting the right, safety and well-being of the subject participant in the trial. So, the results of clinical studies are more credible, and authenticate.

But, some of regulatory amendments become a challenge for Research Industries and its stakeholders. Hence, this study identifies following things:

- *Reason of Regulatory amendment in India*
- *Comparative study between previous and amended regulation*
- *Impact of this Regulatory amendment on Subject's protection, Research Industry and Stakeholder (includes Sponsors/Investors, Industry, Investigators and Ethic Committee*)

Introduction

In the past decade, India had emerged as a preferred site for drug trials by multinational pharmaceutical companies. India is said to have the largest pool of "naive" patients (i.e. untreated) in many disease areas. Clinical Trials Regulations are basically for to protect the health of the citizen of the country. Its objectives are to prevent mortality in enrolled subjects and also to stop illegal trials.

Against illegal trial, a non-governmental organization filed a public interest lawsuit in February 2012, complaining about unregulated clinical trials of new drugs conducted in India by multinational pharmaceutical companies.

On January 3, the Supreme Court heard the complaint and castigated the Union government "for being negligent in curbing illegal clinical trials despite the deaths of at least 2374 persons who had undergone the dubious testing for unregistered drugs between 2007 and 2012. The Court stated 'The drug trials are creating havoc in the country.'

The Centre had admitted that serious adverse events of deaths during the clinical trials in a period of 2005-2012 were 2644, out of which 80 deaths were found to be attributable to the clinical trials,' the affidavit had said. A parliamentary report estimated that currently 150,000 people are enrolled in clinical trials in India. It estimates that between 2009 and 2012, there were 352,475 people in India enrolled in pharmaceutical tests.

Clinical trial on Human subject to evaluate the safety and efficacy of Investigational drugs, but it must consider the safety and well-being of Human Participant, evaluate benefits and risk ratio before providing to the human subject. But in some case, it was not justified or serious lapses existed. For example, In April 2010 the Indian Council of Medical Research suspended a phase V post-license clinical trial of vaccines against the human papillomavirus amid allegations that the trial had violated rules on informed consent. As many as 25, 000 girls in Andhra Pradesh and Gujarat received the vaccine. The violation

came to light when seven girls who received the vaccine died. Subjects were not properly informed about the study.

In India, Drug Controller General of India (DCGI) is the main regulatory authority, which provides approval to conduct clinical trials in India. Along with this Ethics Committee (Institute or Independent) give approval to initiate the clinical study under Institute or Investigator. And the Ethic Committee is having rights to stop a clinical trial in case of misconducting or ask for clarification. But, there is a question mark of the EC as well.

So, Introduced Regulatory Amendment supports all stakeholders to perform their responsibility as per ethical guideline. That helps to protect Human Participant in Clinical Research and make a positive impact on the Clinical Research Industry with credible outcome.

Method and results

India has a young, highly educated workforce and a large population concentrated in an Urban Centers, high prevalence of all major diseased and knowledge of English makes it easy to set up clinical trial sites in India. India is relatively new to the scene contributing to only about 1% of all global clinical trials.

As per the revised Schedule 'Y' of the Drugs & Cosmetic Act (2005), "a clinical trial is a systematic study of new drug(s) in human subject to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamics and pharmacokinetics), and/or adverse effects with the objective of determining the safety and/or efficacy of the new drugs". Clinical trial of drugs is a randomized, single or double blind controlled study in human participants, designed to evaluate prospectively the safety and effectiveness of new drugs/ new formulations.

The new drug as defined under the Drugs and Cosmetic Rules 1945 (D&C Rule), and subsequent amendments include:

- A new chemical entity (NCE)
- A drug which has been approved for a certain indication, by a certain route, in a certain dosage regimen, but which is now proposed to be used for another indication, by another route, or in another dosage regimen.
- A combination of two or more drugs which, although approved individually, are proposed to be combined for the first time in a fixed dose combination (FDC).

Drugs Controller General (India) (DCGI) is equivalent to the US Food and Drug Administration (FDA) and European Medicines Agency (EMEA). The DCGI is the official governing body responsible for all pharmaceutical research and regulatory issues in India described in the Drugs and Cosmetics Rules, 2005 (D&C R). Clinical trials are regulated per Schedule Y of the Drug and Cosmetics Rules.

It has been observed that due to unethical practices, falsified data, noncompliance of GCP guidelines and conducting clinical trials without DCGI approval were some of the existing discrepancies. There are several reports of exploitation of poor, illiterate Indian citizens for clinical trials with increasing reports of trial participant fatalities resulting from the need of strict vigilance and regulations.

Conducting trial in India was easier than in North America or Europe. In India, trial participants were exploited because of illiteracy, poverty and unawareness of basic rights of study participants.

Though, there is a need to promote clinical trials in India, regulations are necessary to ensure safety and well-being of the trial subjects through adequate health insurance and compensations. The Central Drugs Standard Control Organization (CDSCO) has taken a noteworthy step by launching online Clinical Trial Registry –India (CTRI) ensuring accountability, transparency and information sharing on clinical trials in the public domain.

Reason of regulatory amendment in india

Example of Illegal conduct of Clinical Research: Due to Regulatory uncertainty in clinical research hits drug trials in India. An avalanche of reforms to the rules governing the conduct of clinical trials in India has led to an exodus of drug companies and research organizations.

Case 1

- Shirin Abdul Khan was 16 years old when in the year 2009; she was enrolled as a volunteer in a clinical trial to study the effects of adding vitamin D to conventional treatment for patients newly diagnosed with pulmonary tuberculosis. Along with many of her school friends, she was lured by the easy money.
- "It was harmless," Khan says. "We just had to sign a blank form every time the money was given. Whenever I had to go for a check-up, once a month, they would pay us 150 rupees (US$2.50). It was good money for a school student."
- She decided to enroll after hearing about her aunt's treatment for cancer. Sairabano Khan was part of a clinical trial in 2008 to study the safety and efficacy of a new compound for the treatment of multiple myeloma.
- Sairabano Khan received 700 rupees (US$11.00) at home each time she went for a check-up at the Deenanath Mangeshkar Hospital in Pune. This was one month's pay for someone who used to do household chores. She had to stop work because of her illness, and the trial money helped her make ends meet.

There are many such cases in India of money changing hands as volunteers enrolled in trials. However, the companies failed to seek adequate consent from participants in some trials. Sometimes the consent papers were in English, which most patients in rural areas cannot understand, and representatives didn't explain the many risks associated with the trial.

- In 2013, India's Supreme Court took action after receiving complaints and public-interest litigation (PIL) petitions filed by non-government organizations (NGOs). All trials of new drugs were subsequently put on hold. However, the Indian government convinced the Supreme Court that the move was not in the interest of patients who needed new drugs.
- The Supreme Court acceded (approval), but imposed a three-tier screening process for all trials. Since then, the Ministry of Health has laid down fresh rules and amended existing legislation to tighten the regulatory control of clinical trials.
- But uncertainty over the new regulatory regime has led pharmaceutical companies and contract research organizations (CROs) to move their clinical trial program elsewhere.
- Since regulations in India were amended in 2005 in a bid to liberalize the conduct of global drug trials, companies have flocked there because of the genetic diversity of the population. However, trials in the country have been plagued by scandal. Government data show that more than 2,600 patients participating in clinical trials in India died between 2005 and 2012, and nearly 12,000 suffered serious adverse effects. Of these, 80 deaths and more than 500 serious adverse effects were directly attributed to the drug being trialed.

Case 2

- It was a 2009 US$3.6m post-licensure observational study, funded by the Bill & Melinda Gates Foundation, which finally prompted regulatory change.
- The Phase V study (Post-License Clinical Trial), which aimed to evaluate the cost and feasibility of introducing the human papillomavirus (HPV) vaccine into the country's universal immunization program, was run by **the Program for Appropriate Technology in Health (PATH),** a non-profit organization based in Seattle (United States**), the Indian Council of Medical Research (ICMR)** in New Delhi, and the **Indian state governments of Andhra Pradesh and Gujarat**.
- The trial, which involved 24,777 adolescent girls in Andhra Pradesh and Gujrat received the vaccine, was halted by the ICMR in April 2010 following media reports of the deaths of seven participants and a memorandum from '68 human rights and women's groups' send to the Indian Minister of Health and Family Welfare opposing the trial's "unethical" nature. The trial had violated rules of Informed Consent.

- "The media came down hard," says Chandra M Gulhati, a healthcare activist in New Delhi and editor of the Indian medical journal *Monthly Index of Medical Specialties*. "The government had to finally concede defeat."
- The deaths were not found to be causally associated with the vaccine. However, VishwaKatoch, director-general of the ICMR, admitted to India's Parliamentary Standing Committee on Health and Family Welfare in April 2010 that the guidelines laid down by the drug controller general of India (DCGI) had not been adhered to during the trial.
- The DCGI works for the health ministry and is responsible for approving new drugs, clinical trials and medical devices, as well as monitor the quality and efficacy of pharmaceutical products on the market.
- After little action by the Indian Government, the women's health activists who had brought the case to the attention of the Indian Parliament filed a PIL petition in the Supreme Court about unethical promotion of the vaccines in the private and the public sector, violation of rules on informed consent and the need to investigate the deaths and adverse events after vaccination.
- Those required to respond to the petition included the DCGI, the ICMR, the states of Andhra Pradesh and Gujarat, PATH International, and the vaccine manufacturers.
- A second petition on the HPV vaccination project was jointly filed by two NGOs -SAMA, a resource group for women and health, and the Karnataka-based Drug Action Forum - and Delhi Science Forum. These petitions came on the back of earlier PIL petitions on clinical trials filed by NGO Swasthya Adhikar Manch, and doctor and whistleblower Anand Rai.
- In a report published in August 2013, the Parliamentary Standing Committee on Health and Family Welfare said that PATH had violated laws and regulations laid down for clinical trials in India, while conducting the HPV trial, and accused it of promoting the interests of HPV vaccine manufacturers, who would have reaped huge profits had the vaccine been included in the universal immunization program.
- The report was also critical of the ICMR, which forms ethical guidelines for researchers, pointing out that its involvement in the study gave rise to a conflict of interest.
- In a statement, PATH stressed that it strongly disagreed with the findings, conclusions and tone of the report, which it said disregarded the evidence.

Flow chart of case 2

- June 2009: Registration of clinical trials in the Indian Council of Medical Research (ICMR) registry becomes mandatory.
- 2009: Non-profit organization PATH along with the ICMR and two local governments start a phase 4 trial of human papillomavirus vaccine in adolescents in two Indian states.
- April 2010: 68 Indian human rights and women's groups send a memorandum to the Indian Minister of Health and Family Welfare opposing what they say is the unethical nature of the PATH HPV vaccine trial and calling for it to be halted. In response, the ICMR suspends the trial.
- March 2011: Twelve New Drug Advisory Committees are constituted to evaluate applications for approval of clinical trials, excluding investigational new drugs (INDs). Applications for INDs are evaluated by a separate committee.
- February 2012: Indore and Pune based health activist group, SwasthyaAdhikarManch, files Public Interest Litigation seeking justice for "drug trial victims throughout nation".
- January 2013: Amendments to the Drugs and Cosmetics Rules specify procedures to analyze the reports of serious adverse events occurring during clinical trials and procedures for payment of compensation in case of trial-related injury or death.
- February 2013: Amendments to the Drugs and Cosmetics Rules specify various conditions for conduct of clinical trials, authority for conducting clinical trial inspections and actions in case of

non-compliance. Further amendments specify requirements and guidelines for mandatory registration of ethics committees.

- March 2013: The Drugs Controller General of India (DCGI) constitutes an expert committee to examine reports of deaths in clinical trials.
- July 2013: The Ranjit Roy Chaudhury panel — established to advise on policy guidelines for approval of new drugs, clinical trials and banning of drugs — publishes a report suggesting major changes, including that clinical trials should be held only at centers that are accredited for the purpose, and that the existing 12 drug advisory committees should be replaced by a single broad expertise-based Technical Review Committee to ensure speedy clearance of applications.
- July 2013: The US National Institutes of Health announces it is suspending 40 clinical trials in India because of the uncertainties posed by the new requirements.
- August 2013: Parliamentary Standing Committee on Health and Family Welfare publishes report criticizing PATH, the Indian Council of Medical Research and the DCGI over conduct of the HPV vaccine trial.
- August 2013: Drugs and Cosmetics (Amendment) Bill 2013 introduced in Parliament, which contains penal provisions for violations of clinical trial procedures, and provisions for payment of compensation and ethics committees.
- August 2013: The DCGI makes it mandatory for the sponsor or his representatives to furnish the details of the contract between the sponsor and the investigator with regard to financial support, fees, honorarium, and payments in kind to be paid to the investigator.
- September 2013: India's Supreme Court suspends all clinical trials of new drugs in the country.
- September 2013: Contract research organization Quintiles closes its research center in Hyderabad, a joint venture with Apollo Hospitals Enterprise.
- November 2013: The DCGI issues a directive that an audiovisual recording of the process of obtaining written informed consent is required for each trial subject.
- January 2015: The health ministry proposes pre-submission meetings in a bid to enable technical deliberations between stakeholders and the drug regulator before clinical trial applications are submitted.

Other issues

- **Ssues with regard to the ethics committee**, Mr. Amar Jasani, a researcher and trainer in the field of bioethics and public health mentioned that "Ethics committees are the front line regulators for clinical trials. If they were functional, they would be a major factor in preventing unethical trials. The problem is the ethics committees are completely controlled by the institutions-they are not at all independent, the people on the committees are not trained, nor do they have the resources or independence to do their job."

According to Jasani, Indian law allows for commercial ethics committees to be hired by the many CROs they are meant to monitor. "There's a double conflict-of-interest," he said. "They are governed by the CROs or the pharma companies. At the same time they are profit making-so they are more motivated by financial interest rather than the safety of participants."

- **Compensation is another contentious issue** that is being dealt with in the new directive. Between 2010- 2012, the Drugs Controller General had approved 1,065 clinical trials. Activists say that taking advantage of poverty, illiteracy and lack of awareness, pharmaceutical companies or middlemen, even doctors, often connive to deny compensation to participants when due.

The report clarifies: "Compensation need not be paid for injury or death due to totally proven unrelated causes. In all other cases of death or injury/disability, compensation should be paid to the participant or his legal heirs." The base amount and other calculations are still being worked out. Because of this, the Regulation was also amended in term to provide compensation for participating.

- **Informed consenting is also an important issue informed consent is a main part of clinical** Study by which subject confirms his/her willingness to be a part of clinical studies after having been informed about the various components of the study. But non-compliances also have been seen in this area. For example: "Informed consent from each participant is a mandatory prerequisite for a clinical trial," the CIDSCO report emphasizes. This is an area that unethical practitioners have been taking advantage of, Mishra said "For example, the 16-page directive on this count is translated into local Hindi language that fits into a single page, and that too improperly translated. In Indore, at least 95 percent of participants did not know what it was all about and signed."

So, amended new regulation will provide a frame to properly conduct clinical studies in India. New amendments are being made by government to provide benefits to subject and generate truthful, credible data. It is expected, Regulatory amendment in India will give new and effective rules for subject. Hence, Subject rights can never compromise and subject can get proper informing about inform consent, so he/she can take to participate in trial freely.

Comparative study between previous and amended regulation

Regulatory Amendment: All amendments to Clinical research, regulation are explained here with their comparative study from pervious to Recent.

1) **Regulatory amendment in informed consent process**

Informed consent is a main safeguard for the protection of human subjects in research. It is a process it takes decision of whether or not to participate in a study.

"Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form."

The two key words in the definition are 'Voluntarily' and 'informed' are the cornerstone of ethical conduct in clinical research and also protect the rights and safety of the trial subjects.

Previous

- As per schedule Y, in all trials, a freely given, informed, written consent is to be obtained from each study subject. No person can involve in Clinical research as Research Subjects without signed Informed consent.
- The investigator must provide information about the study verbally as well as using a patient information sheet, in a language that is non-technical and understandable by the study subject.
- Informed about all Risk and Benefit ratio, about trial medicine and visits, Subject rights and more as per Protocol and applicable regulatory requirement
- The Subject's consent must be obtained in writing using an 'informed Consent Form'. If the subject or his/her LAR is unable to read/Write – an impartial witness should be present during the entire informed consent process who must append his/her signatures to the consent form.

But, due to non-compliance of this process creates uneventful condition, which make major hazard to subject life or make a serious adverse event.

Example

A phase V trial, which involved 24,777 adolescent girls in Andhra Pradesh and Gujrat received the vaccine, was halted by the ICMR in April 2010 following media reports of the deaths of seven participants because the trial had violated rules of Informed Consent.

Issue with ICF translation also makes major problem like the 16-page directive on this count is translated into local Hindi language that fits into a single page, and that too improperly translated. In Indore, at least 95 percent of research participants did not know what it was all about and signed.

ICF PROCESS Amendment in year 2013

- In the case W.P. (C) No. 33/2012 of SwasthyaAdhikarManch, Indore & Anr Vs. Ministry of Health and Family Welfare &Ors. With WP (c) No. 779/2012 regarding clinical trials.
- The Hon'ble Supreme Court, has passed an order dated 21.10.2013.
- As per the said order, in respect of 5 Global Clinical Trials for which approval was given by CDSCO after 01.01.2013 till 31.08.2013, before the clinical trials are conducted, ensures that audio-visual recording of the informed consent process of the Participants is done and the documentation preserver, adhering to the principles of confidentiality.
- In light of the above order of the Hon'ble Supreme Court, CDSCO vide F. No. GCT/20/SC/Clin./2013 DCGI dated 19.11.2013 has issued direction that in all clinical trials, in addition to the requirement of obtaining written informed consent, audio-visual recording of the informed consent process of each trial subject, including the procedure of providing information to the subject and his/her understanding in such consent is required to be done while adhering to the principle of confidentiality.
- Such audio-visual recording and related documentation would be preserved. This is applicable to the new subjects to be enrolled in all clinical trials including Global clinical trials.

ICF PROCESS Amendment in year 2015

As per Drug & Cosmetics rules, Notification Dated 31stJul2015 of the Government of India in the Ministry of Health and Family welfare (Department of Health and Family Welfare), number G.S.R. 364 (E) the Gazette of India, Extraordinary, Part II, section 3, sub-section (i). The rules may be called the Drugs and Cosmetics (Fifth Amendment) Rules, 2015. Amendment in the Drugs and Cosmetics Rules, 1945, in Schedule Y-

In paragraph 2 under the heading "Clinical Trial", in sub-paragraph (4) relating to "Informed Consent", after clause (iii), the following shall be inserted, namely:-

"(iv). An audio-video recording of the informed consent process in the case of vulnerable subjects in clinical trials of New Chemical Entity or New Molecular Entity, including procedure of providing information to the subject and his understanding on such consent, shall be maintained by the investigator for record.

Provided that in case of clinical trial of anti-HIV and anti-Leprosy drugs, only audio recording of the informed consent process of individual subject including the procedure of providing information to the subject and his understanding on such consent shall be maintained by the investigator for record."

2) Regulatory amendment in 'essential elements' of informed consent

Previous:

a. Essential Elements

1) Statement that the study involves research and explanation of the purpose of the research
2) Expected duration of the Subject's participation
3) Description of the procedures to be followed, including all invasive procedure
4) Description of any reasonably foreseeable risks or discomforts to the Subject
5) Description of any benefits to the Subject or others reasonably expected from research. If no benefit is expected Subject should be made aware of this
6) Disclosure of specific appropriate alternative procedures or therapies available to the Subjects
7) Statement describing the extent to which confidentiality of records identifying the subject will be maintained and who will have access to Subject's medical records
8) Trial treatment schedules (s) and the probability for random assignment to each treatment (for randomized trials)
9) Compensation and /or treatment (s) available to the Subject in the event of a trial-related injury

10) An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury
11) The anticipated prorated payment, in any, to the Subject for participating in the trial
12) Subject's responsibilities on participation in the trial
13) Statement that participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which is Subject is otherwise entitled
14) Any other pertinent information

Amendment in 'Essential Element' of informed consent in year 2013

Amendment in Scheduled Y (Drug and Cosmetic Act) dated Nov'2013; in Appendix V, Under the heading "INFORMED CONSENT", and in sub-heading 1.1 relating to "Essential Elements", for serial number 9 amended as follow:

"9. Statement describing the financial compensation and medical management as under:

a. In the event of an injury occurring to the clinical trial subject, such subject shall be provided free medical management as long as required.
b. In the event of a trial related injury or death, the Sponsor or his representative, whosoever has obtained permission from the licensing Authority for conduct of the clinical trial, shall provide financial compensation for the injury or death."

Amendment in 'Essential Element' of informed consent in year 2015

In APPENDIX V, under the heading 'INFORMED CONSENT' in sub-heading 1.1 relating to 'Essential Elements', following serial number shall be substituted, namely:

"9. Statement describing the financial compensation and medical management as under:

a. In case of an injury occurring to the subject during the clinical trial, free medical management shall be given as long as required or till such time it is established that the injury is not related to the clinical trial, whichever is earlier.

14. Statement that there is a possibility of failure of investigational product to provide intended therapeutic effect.
15. Statement that in the case of placebo controlled trial, the placebo administered to the subjects shall not have any therapeutic effect.
16. Any other pertinent information."

3) Regulatory amendment in serious adverse event reporting and timeframe

Previous SAE and timeframe

- Serious Adverse Event is any untoward medical occurrence that at any dose :
- Result of death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Result in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- Investigator report SAE to Sponsor within 24 hour and to Ethic committee within 7 Working days of SAE Occurrence.
- Sponsor must send report of SAE within 14 Calendar days to DCGI and other participating Investigators of SAE Occurrence.

Amendment SAE and timeframe in year 2013

- The Drugs & Cosmetics Rules have been amended vide GSR no 53 (E) dated 30-01-2013 inserting a Rule 122DAB, and a new Appendix-XII in Schedule Y along with other amendments.

- The amendments specifies the detail procedures for analysis of Serious Adverse Events (SAEs) including deaths occurring during clinical trial to arrive at the cause of death / injury to the subject, as the case may be, and to determine the quantum of compensation, if any to be paid by the sponsor or his representative whosoever have obtained permission from CDSCO in a time bound manner.
- As per the provisions, each SAE including death is required to be examined and decision regarding causality of death and quantum of compensation, if any, is required to be taken by CDSCO in a time bound manner as per the procedure specified in Appendix XII of Schedule Y.
- As per Appendix XII the Investigator shall report all serious and unexpected adverse events to the CDSCO, the Sponsor or his representative whosoever had obtained permission from the CDSCO for conduct of the clinical trial and the Ethics Committee, within twenty four hours of their occurrence.
- In case of serious adverse events of death, the reports shall be examined by an independent Expert Committee constituted by DCG(I) to determine if the cause of death is due to following reasons, which are considered as clinical trial related death and gives its recommendation to CDSCO. In case of clinical trial related death the committee shall also recommend the quantum of compensation to be paid by the sponsor or his representative, to CDSCO.

1) Adverse effect of investigational product(s);
2) Violation of the approved protocol, 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 a placebo-controlled trial;
5) Adverse effects due to concomitant medication excluding standard care, necessitated as part of approved protocol;
6) For injury to a child in–utero because of the participation of parent in clinical trial;
7) Any clinical trial procedures involved in the study

- CDSCO shall consider the recommendations of the Expert Committee and shall determine the cause of death and also the quantum of compensation in case of clinical trial related death within three months of receiving the report of SAE of death.

In cases of serious adverse event other than death, CDSCO shall determine the cause of injury, if any, due to any of the reasons mentioned above as in the case of death, which is considered as clinical trial related injury. However CDSCO has option to constitute an independent Expert Committee, wherever considered necessary, to examine such serious adverse event. In case of clinical trial related injury, CDSCO shall also determine the quantum of compensation within three months of receiving of the SAE.

- In case of clinical trial related injury or death, the Sponsor or his representative concerned shall pay the compensation as per the order of CDSCO within thirty days of the receipt of such order.
- In order to streamline the submission of reports of SAEs, a system of pre-screening of reports of SAEs at the time of receiving these reports is being introduced in CDSCO.

The pre-screening system will be as under

- The preliminary scrutiny of the SAE reports will be done by CDSCO officer(s) based on laid down checklist which is attached herewith. During the preliminary examination, the CDSCO officer(s) will scrutinize the SAE reports to ensure that it contains all the required administrative as well as technical information in proper manner as per the checklist. If SAE reports are not submitted in accordance with the format and the checklist, it will not be accepted by CDSCO for further examination.
- Once a report of SAE is accepted, the information in the report will be reviewed by CDSCO as per the specified procedures.

- The sponsor or his representative conducting clinical trials in India are requested to prepare the SAE reports for submission to CDSCO as per appendix-XI of Schedule-Y of D&C Rules and the checklist enclosed.
- The SAE reports must be submitted with proper binding, indexing and page number. Without indexing of page number, no SAE report will be accepted.

(a) The reports of SAEs of deaths should be prepared and submitted in red cover.

(b) The reports of SAE of injury other than deaths should be prepared and submitted in blue cover.

(c) The SAE report other than that mentioned at (a) & (b) above is to be prepared and submitted in white cover.

- Clear and unequivocal information should be provided in the SAE report.
- Text and tables should be prepared using margins that allow the document to be printed clearly without losing any information and the left-hand margin should be sufficiently large so that information is not obscured by the method of binding. The documents printed on both sides of a page, can be submitted. However, one should take care that the information is not obscured when the page is placed in a binder.
- While submitting reply to a query, the applicant should always enclose with the reply, a copy of query letter issued by CDSCO.
- All items mentioned in the checklist may not be applicable in all the case of SAE‟s. The items not relevant to a particular SAE should be marked with "Not Applicable (NA)".

This system of preliminary screening to determine the acceptability of the SAE report will come into effect from **18.02.2013**

Amendment SAE and timeframe in year 2014

- As per Notification of Ministry of Health and Family welfare (Department of Health and Family welfare) dated **12th Dec, 2014.** GSR 889(E), whereas a certain rules further to amend the Drugs and Cosmetic Rules, 1945 was published. These rules may be called the Drugs and Cosmetics (Sixth Amendment) Rules, 2014.

In the drugs and cosmetics Rules, 1945-

In rule 122DAB-

- For sub-rule (1), the following sub-rule shall be substituted, namely:-

"(1) In case of an injury occurring to the subject during the clinical trial, free medical management shall be given as long as required or till such time it is established that the injury is not related to the clinical trial, whichever is earlier."

- After sub-rule (2), the following sub-rule shall be inserted, namely:-

"(2A) In case, there is no permanent injury, the quantum of compensation shall be commensurate with the nature of the non-permanent injury and loss of wages of the subject."

- In sub-rule (5)

In clause (c), after the words "therapeutic effect", the words, "where, the standard care, though available, was not provided to the subject as per the clinical trial protocol" shall be inserted;

In clause (d), after the words, "Placebo controlled trial", the words, "where, the standard care, though available, was not provided to the subject as per the clinical trial protocol" shall be inserted;

In schedule Y

- In paragraph 2 relating to 'CLINICAL TRIAL',

In sub-paragraph (2), relating to 'Responsibilities of Sponsor', for clause (iv), the following clause shall be substituted, namely:-

"(iv) Any report of the serious adverse event, after due analysis shall be forwarded by the sponsor the Licensing Authority as referred to in Clause (b) of rule 21, the Chairman of the Ethics Committee and the head of the institution where the trial has been conducted, within fourteen days of the occurrence of the serious adverse event."

- In sub-paragraph (3), relating to 'Responsibilities of the Investigator(s)', in clause (i), for the portion beginning with the words "The report of the serious adverse event of death" and ending with the words " occurrence of the serious adverse event.", the following shall be substituted, namely:-

"In case, the investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the Licensing Authority along with the report of the serious adverse event. The report of the serious adverse event, after due analysis, shall be forwarded by the Investigator to the Licensing Authority as referred to in cause (b) of rule 21, the chairman of the Ethics Committee and the Head of the Institution where the trial has been conducted within fourteen days of the occurrence of the serious adverse event."

- In sub-paragraph (5), relating to 'Responsibilities of the Ethics Committee', for clause (iv), the following clause shall be substituted, namely:-

"(iv) In case of serious adverse event occurring to the clinical trial subject, the Ethics Committee shall forward its report on the serious adverse event, after due analysis, along with its opinion on the financial compensation, if any, to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority as referred to thein clause (b) of rule 21 for conducting the clinical trial, to the Licensing Authority within Thirty days of the occurrence of the serious adverse event."

- In sub-paragraph 5(A), relating to 'Serious Adverse Events', in clause (2).-

The Words "and unexpected" shall be omitted;

After the words "and pass orders as deemed necessary", the following shall be inserted, namely:-

"In case, the investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the Licensing Authority along with the report of the serious adverse event."

In Appendix V, in serial number 1, in item number 1.1, in sub-item number 9, for clause (a), the following clause shall be substituted, namely:-

"(a) in case of an injury occurring to the subject during the clinical trial, free medical management shall be given as long as required or till such time it is established that the injury is not related to the clinical trial, whichever is earlier."

In Appendix XII, For serial number (1), the following shall be substituted, namely

"(1) In case of an injury occurring to the subject during the clinical trial, free medical management shall be given as long as required or till such time it is established that the injury is not related to the clinical trial whichever is earlier."

- In serial number (2) after the words, "medical management of the subject", the words, " In case, there is no permanent injury, the quantum of compensation shall be commensurate with the nature of the non-permanent injury and loss of wages" shall be inserted;
- In serial number (5)-

In clause (d), after the words, "therapeutic effect", the words, "where, the standard care, though available, was not provided to the subject as per the clinical trial protocol" shall be inserted;

In clause (e), after the words 'placebo-controlled trial', the words, "where, the standard care, though available, was not provided to the subject as per the clinical trial protocol" shall be inserted;

- In serial number (6),-

In clause (a),

The words, "and unexpected" shall be omitted

After the words "occurrence as per Appendix XI.", the following shall be inserted, namely:-

"In case, the investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the Licensing Authority along with the report of the serious adverse event."

- In clause (b), in Para (i).

- In sub-para (B)-

The words, “chairman of the Expert Committee with a copy of the report to”, shall be omitted;
For the words “ten calendar days”, the word “fourteen days” shall be substituted;

- In sub-paragraph (C)-

The words “to the Chairman of the Expert Committee with a copy of the report”, shall be omitted;
For the words “twenty-one calendar days”, the words “thirty days shall be substituted;
After the sub-paragraph (C), the following shall be inserted, namely:-

“(CA) The Licensing Authority shall forward the report of the Investigator, Sponsor or his representative whosesoever had obtained permission from the Licensing Authority for conducting clinical trial and the Ethics Committee to the Chairman of the Expert Committee.”

- In sub-paragraph (D), for the words “thirty days of receiving the reports from the Ethics Committee” the words, “one hundred and five days of the occurrence of the adverse event” shall be substituted;
- In sub-paragraph (G), for the words “three months of receiving the report of the serious adverse event”, the words, “one hundred and fifty days of the occurrence of the adverse event” shall be substituted;
- In para number (ii),-
- In sub-paragraph (A), for the word “ten calendar days”, the words, “fourteen days” shall be substituted;
- In sub-paragraph (B), for the words “twenty one calendar days”, the words, “thirty days” shall be substituted;
- In sub-paragraph (D), for the words, “three months of receiving the report of the serious adverse event”, the words, one hundred and fifty days of the occurrence of the adverse event shall be substituted.

4) Regulatory amendment of EC registration in feb’2013

- Drug and Cosmetic Rule amendment vide GSR no. 72 (E) dated 08-Feb-2013 inserting Rule 122DD, in Schedule Y along with other amendments. The amendment specifics the detail procedure for the registration of Ethic Committee.
- As per Rule 122 DD, No Ethic Committee shall review and accord its approval to Clinical Trial Protocol without prior Registration with DCG (I). An application for registration of the Ethic Committee shall be made to the DCG (I) in accordance with the requirement as specified in the Appendix VIII of Schedule Y.
- In order to streamline the submission of application for registration of Ethics Committee and their examination as per Rule 122DD, it has been decided to introduce a system of preliminary scrutiny of such applications at the time of their receipt, to determine their acceptability for examination by CDSCO.

5) Number of clinical studies conduct by investigator jul’2014

- As per DCGI recommendation, the sponsor shall ensure that the number of Clinical Trial an investigator can undertake should be commensurate with the natures of the trial, facility available with the Investigator. However, under no circumstances the number of trials should be more than three at a time. Effective Date 03-Jul-2014
- **Re-Amendment Aug’2016:** Removal of Restriction of conducting 3 clinical trials per Investigator. Effective date 02 Aug 2016

Brief chart of clinical research amendment in form year 2013 to Nov' 2016

Document Name	File Name/ Order #	Effective date
Removal of Restriction of conducting 3 clinical trials per Investigator. Effective date 02 Aug 2016	File No.12-01/14-DC(Pt.47)	2-Aug-16
Removal of condition for the requirement of 50 Bedded site from clinical Trial. Effective date 02 Aug 2016	File No.12-01/14-DC(Pt.47)	2-Aug-16
Requirement of NOC form DCGI for addition of new clinical trial site or investigator. Effective date 03 Aug 2016	File No.12-01/14-DC(Pt.47)	3-Aug-16
A-V Consenting in case of Vulnerable subjects for ICF	GSR 611(E)	31-Jul-15
SAE Compensation and SAE reporting time line	GSR. 889 (E)	12-Dec-14
Providing Ancillary care for CT Subject	File No.12-01/14-DC(Pt.47)	3-Jul-14
Clinical Trial on Medical Device	File No.12-01/14-DC(Pt.47)	3-Jul-14
Requirement for Filing of application to market new Chemical Entities	File No.12-01/14-DC(Pt.47)	3-Jul-14
Limited number of clinical trial an Investigator	File No.12-01/14-DC(Pt.47)	3-Jul-14
CT-Compensation in case of Injury or Death	File No.12-01/14-DC(Pt.47)	3-Jul-14
A-V consenting of each trial Subject	GCT/20/SC/Clin./2013	19-Nov-13
EC Registration	G.S.R 72(E)	8-Feb-13
Submission of Report of SAEs to CDSCO	GSR no 53 (E)	30-Jan-13

Impact of regulatory amendment on subject's protection/ clinical research industry/ stake holders

Evaluation the result of regulatory amendment

For evaluating the impact of the regulatory amendment on Human Subject, Research Industry and Stakeholders; I preferred to ask questions from personnel who are active parts of the clinical research process and conduct clinical trials like: Investors, different department in Clinical Research Organization (Operation, Regulatory Record, Data Management, Safety and others) and Investigators. With these feedbacks, Result of Regulations Amendment can identify. Here, I will explain the impact of the amendment with feedback.

1) Serious adverse event report and timeframe

- **SAE Compensation, reporting and system of pre-screening for submission of report toCDSCO [In 30JAN2013, File no. 12-01/13-DC (Pt.13-A)]**
- Inserting a rule 122DAB and new Appendix-XII in Schedule 'Y'
- The amendment specifies the detail process for analysis of SAEs include deaths and Injury during clinical trial and determine the quantum of compensation to be paid by Sponsor and his representative
- In this amendment, CDSCO has Changed all stakeholder timelines and structure of reporting SAEs
- In case of Death, the report examined by the Independent Expert Committee (constituted by DCGI) determines the cause of death and this committee also recommends the quantum of compensation to be paid by the sponsor and his representative.
- CDSCO has constituted an independent Expert committee in case of death and injury, shall determine the quantum of compensation within three months of receiving of the SAE.
- In case of Clinical trial related injury or death, the sponsor or his representative shall pay the compensation within 30 days of receipt of such order.
- This regulation also provides a checklist by which CDSCO officer can scrutiny of SAE reports.
- **Feedback:** Overall feedback of this regulation was Negative due to following reason:
- Quantum of compensation will decide by the Independent Expert Committee, no any guideline was available for calculation of quantum of compensation. Sponsor and his representative need to follow Expert committee decision.
- Due to undefined expanse, this regulation impacting negative, as this is something extra expenses will come over the sponsor.
- Reporting to Independent expert committee, involving Unexpected SAE, provide less time in reporting also giving Negative impact of this regulation.
- **SAE Compensation and reporting timeline [In 12Dec2014, File GSR.889(E)]:**
- With consider the above response, CDSCO make amendment in D&C act, after doing consultation with the Drugs Technical Advisory Board.
- In rule 122DAB- (1) In case of any injury occurring to the subject during the clinical trial, free medical management shall be given as long as required or till such time it is established that the injury is not related to the clinical trial, whichever is earlier.
- After Sub-rule (2), '2A-In case, there is no permanent injury, the quantum of compensation shall be commensurate with the nature of the non-permanent injury and loss of wages of the subject.
- Direct sending SAE report to Expert Committee has omitted.
- Timeline of reporting has modified/increased for all stakeholders after due analysis.

For Sponsor, report sent duration increase from 10 Calendar days to 14 days to License Authority, EC and Head of Institute where trial has conducted.

For Investigator, Unexpected adverse event and direct report to Expert Committee has omitted. After a due analysis report duration has changed from 10 days to 14 days.

For EC, After due analysis SAE reporting timeline has changed to 21 days to 30 Calendar days.

Feedback: Points which were negative, now it's become Positive after this Amendment.

- Positive response received as Unexpected SAE has omitted, Time frame increase for due analysis, direct reporting to Expect committee has omitted.
- The response received, the report can evaluate properly and correct report forwarded to License Authority and other stakeholder.
- On 03JUL2014, Guideline "CT-Compensation in case of Injury or Death" also introduced by CDSCO. This guideline is available for calculating Quantum of compensation. So, Investor and other stakeholder can calculate it. The unpredictable cost issue has also been resolved with this.

2) Informed consent process of subjects

- **A-V consenting of each subject of each trial Subject [In19Nov2013, File number GCT/20/SC/Clin./2013]:**

- In case W.P. (c) No. 33/2012 of SwasthyaadhikarManch, Indore &Anr Vs. Ministry of Health and Gamily welfare &Ors., the Hon'ble Supreme Court, has passed an order dated 21.10.2013. Before the clinical trials are conducted, Audio-Visual recording of the informed consent process of the Participants should perform of each subject.
- Add Essential elements in Informed consent Form, hence subject gets informed about detail description and requirement of Clinical Trial.
- Storage of A-V consent at least a period of 5 years if it is not possible to maintain the same permanently.

Feedback: Received Negative feedback about this amendment.

- Most of the subjects were not ready for A-V consenting, as subject feeling uncomfortable with this process.
- As received feedback from Investigator and Research Coordinator, Subject's start feeling afraid and makes negative perception about clinical research, before any explanation about research.
- In leprosy or HIV trial or any major critical illness, it becomes difficult to take an audio-video consenting with Subject and his/her legal representative, as they don't want such consenting due to embarrass feeling.
- Due to this expected number of subjects in Clinical trial was not matched, putting negative impression of this amendment and affect the growth of Clinical Market as well.
- Due to this regulation, many investigators don't want to involve and process of Informed consent process due to undefined fear factors.
- Audio-Visual consenting is a time consuming and lengthy procedure.
- For this site need specific set-up where they can seat and defined or described all point to subject
- Storage of consent was also an issue for some investigator or Clinical Coordinator in some place.
- **A-V Consenting in case of vulnerable subjects[In 31Jul2015, GSR 611(E)]:**
- These rules called the Drug and Cosmetic (Fifth Amendment) Rules, 2015.
- In paragraph 2 under heading 'Clinical Trial', in sub-paragraph (4) relating to 'Informed Consent', after clause (iii)-

(iv) An audio – video recording of the informed consent process in the case of vulnerable subjects in clinical trials of New Chemical Entity or New Molecular Entity including procedure of providing information to the subject and his understanding on such consent, shall be maintained by the investigator for the record.

- Provided that in case of a clinical trial of anti-HIV and anti-Leprosy drugs, only audio recording of the informed consent process of individual subjects, including the procedure of providing information on the subject and his understanding on such consent shall be maintained by the investigator for record.
- Modified and add in Sch. Y, Appendix V, under heading 'Informed Consent'-

14) Statement that there is a possibility of failure of Investigational product to provide intended therapeutic effect

15) Statement that in the case of placebo controlled trial, the placebo administered to the subjects shall not have any therapeutic effect.

Feedback: Received Positive feedback

- A-V consenting to each subject (on 19Nov'2013), provide a Negative impact on stakeholder of this amendment, but this negative impression turns to Positive with amendment of A-V Consenting in case of Vulnerable Subjects for ICF.

- Now, with this amendment, Subject feels comfortable to be a part of Clinical study. Anti-HIV and Anti-Leprosy also not feeling embarrassed to be a part of the study, as they go with the audio consenting process in case of New Chemical Entity or New Molecular entity.

3) Ethic committee registration [In 08Feb2013, file number GSR 72 (E)]

- Insert rule 122 DD, Registration of Ethics committee with the requirements as specified in Appendix VIII of Schedule Y.
- So, No Ethic Committee shall review and accord its approval of a clinical trial protocol without prior registration with the Licensing authority.
- In case of SAE occurring to the subjects during clinical trial, the EC shall analyze and forward its opinion as per procedure specified in Appendix XII of Sch. Y
- Registration valid for a period of Three years from the date of Issue, so Ethic Committee will apply for re-registration by License Authority before expiry.
- **Feedback:** Received Positive feedback about this amendment.
- Registration of the EC by CDSCO, gives positive impact among all stakeholders.
- It's helpful to conduct research under surveillance and protect trial subject's rights, safety as well.
- Now, EC actively involved in site activities and issues. Like-
- As per CDSCO regulation on 02Aug2016, **Removal of Restriction of conducting 3 clinical trials per Investigator;** it is further decided that an Ethic Committee after examining the risk and complexity involved in the trial being conducted/proposed shall decide about how many trials an investigator can undertake.
- As per CDSCO regulation on 02Aug2016, **Removal of condition for the requirement of 50 Bedded sites from clinical Trial;** regard to this amendment, No clinical trial shall be conducted on site having less than 50 bedded hospitals, it has been decided to revise this condition and it is further decided that Ethics Committee shall examine and decide whether the clinical trial site is suitable for trial or not irrespective of number of beds.

So, as per received feedback, overall impact about the Clinical Research Regulatory Amendment is positive and Effective in term of:

- Conduct clinical research with proper regulation become mandatory
- Protecting the rights, safety and well-being of Trials Subjects become more strong and effective
- During Informed consent process, Subject rights to know all risk and benefit of study and subject is free to take decision to participate in the study.
- Protection of study subjects are more secured due to effective reporting of SAE and Compensation guideline
- Site, including Investigator and Coordinator must perform their responsibility as per regulation
- Ethic committee become more responsible to regulate clinical trial on site in positive term, that help to take decision and action against any discrepancy on site level
- All regulations are well instructed and written, that make clear understanding and view for investors to conduct clinical research in India.
- With all effective regulation, investors become aware and secure to get effective, credible and authenticated clinical data and good protection of human participant in a Clinical Trial.
- It is expected as per received feedback and response, these regulations help to improve:
- Subject safety during clinical trial
- Increase interest of Stakeholder toward India and ultimately it will give growth to Clinical research market in the near future in India.

Conclusion

The updated guidance on conducting clinical trials in India is steadily improving, as DCGI is committed to amend and upgrade the policies to encourage research in India. This emerging trend in clinical research indicates broad based effectiveness oriented approach.

The road was bumpy and there were lots of hurdles. The recent regulatory amendments give a fresh breath of air to the Clinical Research industry, which was gripped by ethical issues and non-transparency. Most of the issues have resolved in the past few years and also successful to cover the loopholes in the regulations and make India a trial and patient friendly global destination.

In recent years, Indian regulatory authorities have been quite aggressively working toward all fronts, with the goal of enhancing the quality and integrity of research through optimization of approval timelines. The stringent process for both regulatory approval and patient recruitment had a severe impact on the clinical research industry.

The Indian clinical research industry booms up, with implementation of all regulatory amendments made by CDSCO. It will make a drastic change or growth in the Indian clinical research market in near future.

Reference

[1]. http://www.cdsco.nic.in/forms/list.aspx?lid=1585&Id=1

[2]. Sama: Resource Group for Women and Health. Memorandum to the Health Minister on World Health Day opposing HPV vaccinations. April 2010.

[3]. Department of Health Research, Ministry of Health and Family Welfare. Seventy-second report on alleged irregularities in the conduct of studies using Human Papillomavirus (HPV) vaccine by PATH in India. August 2013.

[4]. Report of Professor Ranjit Roy Chaudhury expert committee to formulate policy and guidelines for approval of new drugs, clinical trials and banning of drugs. July 2013.

[5]. Pandey A, Aggarwal AR, Seth SD, Maulik M, Bano R, Juneja A. Clinical trials registry—India: redefining the conduct of clinical trials. Indian J Cancer2008;45:79-82.

[6]. Mudur G. Human papillomavirus vaccine project stirs controversy in India. BMJ2010;340:c1775.

[7]. AHRP/cms/content/view/898/84/ (Internet reference about Mr. Amar Jasani statement)

[8]. THE HEALTH SITE/news/no-more-clinical-trials-till-you-can-monitor-them-supreme-court-to-centre/

[9]. JANANEETHI/jananeethi/projectregard/papernews/supremecourt_onclinicaltrial_4-1-12.pdf

[10]. IPSNEWS/2011/10/india-unauthorised-clinical-trials-on-bhopal-victims/

[11]. Dhananjay Mahapatra.2644 died during clinical trails during 7 years, The Times of India, Oct, 2012.

[12]. Hob'ble Mr. Justic R.M. Lodha, Hon'ble Mr. Justic Anil R. Dave. SwasthayaAdhikaManch, Indore & Anr. Vs. Min. of Health & Family Welf. &Ors. WP © 33 OF 2012, ORDER DATED: 3rdJan2013,with W.P.(C) No.79 of 2012, http://courtnic.nic.in/supermecourt/temp/wc%203312p.txt,8.10.2012,26.7.13

[13]. Ethical Guidelines for Biomedical Research on Human Participants Indian Council of Medical Research, New Delhi, 2006

[14]. The Drug and Cosmetic (Amendment) Bill, 2013 (Bill No. LVIII OF 2013)

[15]. The Indian Medical Council (Professional conduct, Ethic & Etiquettes) Regulation, 2002, 7.22 CHAPTER 7 : MISCONDUCT

[16]. Minutes of the meeting of the Ethics Committee held on 20th November, 2012 at 09:00 A.M. in the Council Office, Sector-8 pocket-14, Dwarka, New Delhi-77. Available at: hhtp:www.mciindia.org/meetings/Ethics/2012/Minutes_20.11.2012.pdf

[17]. Pawan Kumar Bansal. Politicians who exposed malpractices in medical sector. Available at: http:www.merines.com/article/plioticians-who-exposeed-mal[ractices-inmedical-sector/15894017.shtml#sthash.ctMh8LEV.Fhc3l1z.dpuf

[18]. 'www.unethicalclinicaltrial.org/Case_studies.aspx' of swasthyaadhikarmanch