CLINICAL RESEARCH LAW, ETHICS AND TECHNO-SCIENCE

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The development of a new drug is a lengthy process once a promising compound is identified it must be investigated in laboratory studies and tested on laboratory animals. After years of work the newly developed drug is ready for clinical trials, or the testing on human volunteer.

Clinical trials (with safeguards) are necessary for introduction of new drugs for a country like India, considering its disease burden and emergence of new variants of diseases. Clinical trials are the only way of establishing the safety and efficacy of any new drug before its introduction in the market for human use.

Trial is derived from the Anglo-French *trier,* meaning *to try.* Broadly, it refers to the action or process of putting something to a test or proof. Clinical is derived from *clinic,* from the French *cliniqu'e* and from the Greek *klinike,* and refers to the practice of caring for the sick at the bedside.

Two ancient Indian scripts Charaka Samhita (a text of medicine) and Sushruta Samhita (a text of book of surgery), complied as early as 200 B.C. and 200 A.D. respectively shows that medical research is not a new concept for India. However, a lot has changed in the clinical research scenario since then. Currently estimated at 500 million US Dollar, India's clinical research market has projected to cross one billion US Dollar mark by 2016 driven by favorable factors like diverse and accessible population, availability of low cost and effective resources.

Science breeds technology and together holds out hope for human happiness worldwide. If misdirected, technology promotes thanatology or science of death. The glory of technology shines when its discoveries

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' Epitome of the LL.D Post-doctoral thesis titled "Clinical Research And Human Experimentation -A Juridical Study"

liberate humans from dogmas and obscurantisms and transforms society as a heaven of joy and security, the fullness of faculties and scientific social order where egalite is writ large in the face of the world order. The choice between science for betterment of humanity and grave peril and incurable suffering of society depends upon wisdom and compassion versus wickedness and torturesome grab of wealth, with greed of the powerful dominating the needs of the victimized vast'. Indeed when life marches, law cannot lag behind. Roscoe Pound, adopting a similar perspective, observed, "all the social sciences must be co-workers, and emphatically, all must be co-workers with jurisprudence." It is thus clear that with the rapid strides science and technology make at a global level. Law cannot remain insular and aloof clinging to ancient precedents but must keep pace with the leap forward at a like pace.' Law is but a part of human conduct, and in the idea of purpose. Ihering found the mainspring of laws, which are only instruments for serving the needs of society. Their purpose is to further and protect the interest of society there is an inevitable conflict between the social interests of man and each individual's interest.

Clinical research sponsored or undertaken by developed countries in developing countries also raises fundamental questions about distributive justice. The discrepancies in power and wealth between developed and developing countries are reflected in the widely differing availability of healthcare resources and the quality of healthcare provision.

To advocate the development of science and technology is one thing, to prioritize it over the sacrosanct notions of autonomy and respect for life in furtherance of commercial interests is quite another one.

The Nuremberg Code 1947 that made voluntary consent a requirement in clinical research studies. The Belmont Report 1949 set forth three underlying ethical principles -respect, beneficence and justice for the volunteers. The Helsinki Declaration makes it mandatory for the medical community to essentially think about the benefit and non benefit research and assess the benefit/ risk ratio before initiating the trials and

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Justice V.R. Krishna Iyer: Science, Religion and The Dharma of Social Development : *Off The bench,* Universal Law Publishing Co. Pvt. Ltd. 2006 p294-295

Justice V.R. Krishna Iyer: Society, Law and Science : *Off The bench,* Universal Law Publishing Co. Pvt. Ltd. 2006 p305-306

International ethical guidelines for Biomedical Research involving Human Subjects by council for International Organisations of medical Sciences (CIOMS) covering interests of local community and appreciation of cultural ethos after internationalization of research.' The Guidelines for Good Clinical Practice is published by the International Conference on Harmonization: Good clinical practice (E6). The statement of **Ethical Guidelines for Biomedical Research on Human Participants:-** The 2000 guidelines state that trial subjects should be fully informed of the research before they consent'. **This is restated more forcefully in the 2006 guidelines:**

"Principles of the maximization of the public interest and of distributive justice whereby the research or experiment and its subsequent applicative use are conducted and used to benefit all human kind and not just those who are socially better off but also the least advantaged; and in particular, the research participants themselves and or the community from which they are drawn." (Principle VIII)

The Helsinki Declaration underwent changes five times, the last one being in 2004. Still the controversy about use of placebo and post-trial access as described in it is being debated. The most recent documents on ethics are those of UNESCO's **"The Universal Declaration on Human Genome and Human Rights"** (1997), **"The International Declaration on Human Gene Data"** (2003) and **"Universal Declaration on Bioethics and Human Rights"** (2005).

Clinical Trial is now, since January 20, 2005, defined in Rule 122 DAA of Drugs and Cosmetics Rules, 1945. The Rules themselves are framed under the Drugs and Cosmetics Act, 1940, the principal statute in

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[4] Clinical trials Commerce Versus Ethics (Pharmabiz.com) (April 6, 2007)

"Any research using the (sic) human beings should be selected so that burdens and benefits of the research are distributed without arbitrariness, discrimination or caprice." Research should abide by the principles of "maximization of the public interest and of distributive justice whereby, the research or experiment and its subsequent applicative use are conducted and used to benefit all humankind and not just those who are socially better off but also the least advantaged, and in particular the research subject themselves". (Principle VIII)

the field.[6] This is a law enacted by Parliament and applies along with the Rules, in the states in the country. Drugs themselves to which the statute applies are defined in Section 3 (b) of the Act.

Rule 122 DAA of Drugs and Cosmetics Rules, 1945 (Since January 20, 2005)- Clinical trial means a systematic study of new drug(s) in human subject(s) to generate data for discovering and /or verifying the clinical, pharmacological (including pharmacodynamic and pharmacolcinetic) and /or adverse effects with the objective of determining safety and / or efficacy of the new drug.

Section 122E of the Drug and Cosmetics Act- 'New Drug' more generally defined in Act as "a drug" which has not been used in the country to any significant extent under the conditions prescribed, recommended or suggested in the labeling thereof ...even if it is not an 'Investigational New Drug.

Rule 122 DA of Drugs and Cosmetics Rules, 1945- (1) No clinical trial for a new drug, whether for clinical investigation or any clinical experiment by any Institution, shall be conducted except under, and in accordance with, the permission in writing of the Licensing Authority defined in clause (b) of rule 21.

These rules may be called the Drugs and Cosmetics (3rd Amendment Rules, 2002). Now, therefore, in exercise of the powers conferred by Sections 12 and 33 of the said Act, the Central Government, after consultation with the Drugs Technical Advisory Board, hereby makes the following rules further to amend the Drugs and Cosmetics Rules, 1945, In the Drugs and Cosmetics Rules, 1945, in rule 69, after sub-rule (5), the following sub-rule should be inserted, namely:- "(6) Where an application under this rule is for the manufacture of drug formulations falling under the purview of new drugs as defined in rule 122-E, such application shall also be accompanied with approval, in writing, in favour of the applicant, from the licensing authority as defined in clause (b) of rule 21." In rule 71 of the said rules, in sub-rule (6), after clause (iv), the following clause shall be inserted, namely:- "(v) have the approval, in writing, in favour of the applicant to manufacture drug formulations falling under the purview of new drug as defined in rule 122-E, from the licensing authority as defined in clause (b) of rule 21.". in rule 75 of the said rules, in sub-rule (5), the following sub-rule shall be inserted, namely:- "(6) Where an application under this rule is for the manufacture of drug formulations falling under the purview of new drug as defined in rule 122-E, such application shall also be accompanied with approval, in writing, in favour of the applicant, from the licensing authority as defined in clause (b) of rule 21.".In rule 76 of the said rules, in sub-rule (7), after clause (iv), the following clause shall be inserted, namely:- "(v) have the approval, in writing, in favour of the applicant to manufacture drug formulations falling under the purview of new drug as defined in rule 122-E, from the licensing authority as defined in clause (b) of rule 21.".

(2) An application for grant of permission to conduct:-

(a) human clinical trials (Phase-I) on a new drug shall be made to the Licensing Authority in Form 44 accompanied by a fee of fifty thousand rupees and such information and data as required under Schedule Y... ..."

Insertion of Rule 122 DAB in the Drugs and Cosmetics Rule, 1945 (called as The Drugs and Cosmetics (First Amendment) Rules, 2013 (1) lays down the requirement of providing free medical management as long as required, in the case of an injury occurring to a clinical trial subject. Further if the injury suffered by the trial subject is related to the clinical trial conducted on such subject, he or she shall also be entitled for financial compensation as per order of the Licensing Authority. In case the clinical trial results in the death of the subject, financial compensation, as per the order of the Licensing authority, has to be compensated to the nominee (s) of the deceased subject. The preceding subsections of the Rule explain the circumstance which is considered as a "direct nexus" to an immediate cause to the injury/death, consequences of non-payment of compensation, etc.

Rule 122 DAC in the Drugs and Cosmetics Rule, 1945 (called as The Drugs and Cosmetics (Second Amendment) Rules, 2013 specifies the prerequisites required for a clinical trial to be considered as adequate so as to grant permission by the Licensing Authority to be conducted on any human body. Further the rule lays down the power of the Licensing Authority to impose any additional conditions to be fulfilled in case of grant of permission in respect of any specific clinical trial, as it is deem fit.

Rule 122 DD in the Drugs and Cosmetics Rule, 1945 (called as The Drugs and Cosmetics (Third Amendment) Rules, 2013 deals with mandatory registration of the Ethics Committee and specifies that no Ethics Committee shall review and accord its approval to a clinical trial protocol without prior registration with the Licensing Authority as defined in clause (b) of rule 21 and describes the procedure of such registration to be made by filling an application to be made to the Licensing Authority in accordance with the requirements as specified in the Appendix VIII of Schedule Y of the Rule and the procedure thereof.

Reported deaths and Amendments: Method for calculating the quantum of financial compensation- For assessing compensation in the case of trial related injury or death following parameters needs to taken into consideration:

a) Age of the deceased;

b) Income of the deceased;

c) Seriousness and severity of the disease, the subject was suffering at the time of his/her participation into the trial.

d) Percentage of permanent disability

Cl = **A x B (1 - F / 100)**

C2 = A x B (1 - F/100) x D /100

Where A is the age of subject, **B** is income of the subject, D is percentage disability caused to the subject due to clinical trial. F represents risk factor a scale of 0 to 100 shall be used for determining the seriousness and severity of the disease.

A report in "The Indian Express"[7] states that, 'Indians are treated as guinea pigs for clinical trials by multinational pharma majors and very few cares to compensate the victims of the trials, reveals data put out by the Union health ministry.'

Till April 2013, only 12 (twelve) clinical trials have been approved by the authority as compared to almost a three digit figure last year. This certainly raises a concern for the future of clinical trials in India- country which once was perceived as a fertile place for growth of clinical trials by most of the multi-national corporations.

It is essential that the Central and State governments put a quick end to this sordid state of affairs. Ensuring the safety of patients is paramount, as more than 1,700 persons have died in clinical trials across the country between 2007 and 2010. A total of 2646 deaths and 14,616 serious adverse events were reported in January 2013 in Supreme Court by the Deputy Drug Controller of India.

Institutional Ethics Committee- As clinical research involves human participants, researchers are ethically obligated to protect them. The two

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[7] The Indian Express, dated 26th September, 2011

principal protections offered to an individual taking part in clinical research are (1) Written Informed Consent and (2) Ethics Committee (EC) review.

Clinical Trials Registry

Clinical Trials Registry-India (CTRI) launched on 20[811]July, 2007. The World Medical Association, in its revision of the Declaration of Helsinki, now specifies that 'every clinical trial must be registered in a publicly accessible database before recruitment of the first subject' .[8] In November 2008, the Drugs Controller General of India (DCGI) started 'advising' all those applying to the DCGI for permission to conduct clinical trials to register their trials.[9] However, the DCGI's decision to make it mandatory for trials initiated after 15 June 2009.

Clinical research and Intellectual property Rights

In 1994, Government signed the agreement on Trade Related Aspects of Intellectual Properties (TRIPS) to provide minimum protection to the Intellectual Property by the member states of World Trade Organization (WTO). India amended the Patent (Amendment) Bill before 2005 and extended its weak process patent to strong TRIPS competent 'Product' patent system for pharmaceutical products. With the increasing faith in the system, companies flooded the market and more global trials came. Lately, to decrease the review time of application from 16 weeks to 10 weeks the CDSCO has introduced the fast tracking of clinical trials in 2006.

Clinical research and Medical Ethics

The Hippocratic ethical principle of *primumnon nocerew* is a time-tested principle that has governed the field of medicine. The Hippocratic Oath specifies the principles of beneficence and non-maleficence and the rule of confidentiality. The doctor-patient relationship based on trust should be esteemed and preserved in our society.

' The Indian Express, dated 26th September, 2011

World Medical Association (WMA). Declaration of Helsinki. Ethical principles for medical research involving human subjects. 59th WMA General Assembly, Seoul, October 2008. Available at http://wwwwma.net/en/30publications/lOpolicies/b3/ index.html (accessed on 10 March 2010).

◦ Pandey A, Aggarwal A, Maulik M, Seth SD. Clinical trial registration gains momentum in India. Indian J Med Res 2009;130:85-6.

10 The first thing is to do no harm.

Principle Based Ethics, T.L. Beauchamp and J.F. Childress have long championed the utility of `Principlism', they hold that ethically appropriate conduct is determined by reference to four key principles which must be taken into account when reflecting on one's behavior towards others.

1. The Principle of respect for individual autonomy (i.e. - individuals must be respected as independent moral agents with the 'right' to choose how to live their own lives).
2. The principle of beneficence (i.e.- one should strive to do good where possible).
3. The principle of non maleficence (i.e. - one should avoid doing no harm to others).
4. The principle of justice (i.e. - people should be treated fairly, although this does not necessarily equate with treating everyone equally). While `principlism' is by no means universally acceptable as the lingua franca of ethics and indeed has been critised as embodying too much of a North American perspective.n

Deontological Ethics: Rights-Based View - Kant's evaluation of any ethical duty required an analysis of whether it was consistent with a "categorical imperative" (which included conduct that was valid without making it conditional upon a purpose). In dealings between human beings, there was only one "categorical imperative" - "Act so that you treat humanity, whether in your own person or in that of another, always as an end, never as a means only.[12]" Kant's theory is, at the same time both individualistic (importance of autonomy) and universal (based on universally valid rules). Thus, the patient can be assured that his best interests will be considered and two justifications for informed consent become evident.

"S. Holmes, Not just autonomy- The principles of biomedical ethics' (1995) 21 J Med Ethics 332 and Takala 'what is wrong with global

[12] Responsibility in Investigations on Human Subjects. Statement by the Medical Research Council 1964

C. Fried, *Medical Experimentation:* Personal Integrity and Social Policy Responsibility in Investigations on Human Participants and Material and on Personal Information, November 1992W. Silverman. "The Myth Of Informed Consent: In Daily Practice and In Clinical Trials", *Journal of Medical Ethics* 1989D. W Vere, "Problems in Controlled Trials - A Critical Response", *Journal of Medical Ethics* 1983R. M. Hare has also stressed the value of aiming at a multi-level ethical system comprising intuitions, principles and background theories. He is quoted by R. Gillon, *Philosophical Medical Ethics op. cit.* I. Kant quoted in Wulff, Pedersen and Rosenburg, *Philosophy of Medicine: An Introduction* M. Baum, Commentary in *Journal of Medical Ethics* 1983

Firstly, a doctor must not coerce the patient and so intrude his bodily integrity and secondly, a patient can only make a rational, reasoned decision when he is aware of the full facts. An illustration of contravention Kantian notion of autonomy" is mentioned in Swasthya Adhikar Manch case" wherein, the mentally disabled were recruited to a trial that was not even catering to the needs specific to their population.

Utilitarian Ethics: Summarily, the utilitarian way of dealing with the conflicting moral dilemmas of RCT's would be in its classic Benthamite form of "greatest good for the greatest number", (or the Felicific Calculus), to justify the sacrifice of the individual to the wider claims of a group. The trials conducted in 2004 by the Bhopal Memorial Hospital serve as another example. Victims were essentially mere instruments that were subjected to trial and practice, to 'serve the greater good'. What possible justification can the physicians of a democratic welfare state give for using the victims of a gas tragedy as guinea pigs?

The word `phannacovigilance' has derived from the Greek word pharmacon means 'drug' and the Latin word vigilare means 'to keep awake or alert, to keep watch. India is the fourth largest producer of pharmaceuticals in the world. It is emerging as an important Clinical trial hub in the world. Many new drugs are being introduced in our country. Therefore, there is a need for a vibrant pharmacovigilance system in the country to protect the population from the potential harm that may be caused by some of these new drugs." Pharmacovigilance has not picked up well in India and the subject is in its infancy. India rates below 1% in pharmacovigilance as against the world rate of 5%.

The Clinical Trial Process and Procedure in India

The Protocol committee (put together by the sponsor), and sometimes editors of journals, review proposed protocols and recommend changes if required. The national drug regulatory body -the Drugs Controller General of India (DCGI) in India and The Food and Drug Administration (FDA) in the US - needs to give approval to start a trial. The ethics board including medical doctors and other biomedical researchers and also people

" wherein a person is an end in himself and he should not be used as means for the welfare of others.

[14] Swasthya Adhikar Manch v. Union of India, WP(C) No. 33 of 2012

[15] P. Biswas, A. K. Biswas Setting standards for proactive pharmacovigilance in India: The way forward. 39:124-128, (2007) 39:124-128, (2007) Indian J Pharmacol.

with completely different expertise, such as lawyers or lay people of an institution hosting a trial also needs to pass the protocol before the trial is initiated. A point to note is that the names and contact information of the subjects are kept strictly confidential and are not conveyed to the sponsors at any time. The research subject needs to give informed consent.Adverse Events get reported to a number of people, to all other Investigators doing the same trial, to all the ethics boards, the steering committee, the Data Safety and Monitoring Board, the local Phannacovigilance committee, the local drug authority and the international one in case it has given permission for the trial.

If there is a pattern to the adverse events over several sites, these will be detected and the trial halted. The Steering Committee is authorized to *`unblind'* a study before it is over, and look for evidence that the drug is safely and effectively working[16].

Regulators: Drug Controller General of India (DCGI)

Trial sponsor must obtain approval from the DCGI before starting a trial & should submit data from pharmacokinetic and animal studies. Phase I trials collect information on the drug, including its safety and adverse reactions. They are usually conducted on a small number of healthy volunteers. Phase II trials evaluate the effectiveness and safety of a drug on patients. Phase III trials are conducted on larger numbers of people to confirm the evidence from earlier phase trials towards obtaining marketing approval of the drug. Phase IV trials are conducted after a drug obtains marketing approval. They are conducted for various purposes including monitoring for drug interactions and testing for new uses of the drug .The regulators may inspect all parties who conduct or oversee clinical research and verify the information submitted to the regulatory authorities.

The Concept of Informed Consent in Clinical Trial: Specific Study of Vulnerable Population

Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault

[16] Ritu Mehdiratta, Deepak Kumar Panda and Gayatri Saberwal, Bio-business in brief: The challenges of Clinical Trials, *Current Science,* Vol. 93, No. 10, 25 November 2007 P1367

[17] Quoted in - Schloendorf v. Society of New York Hospital (1914) 105 NE 92.

valid only if certain conditions are satisfied.'[18]

(i) The patient must be legally competent.

(ii) The consent must be freely given;

(iii) The person consenting must be suitably informed:

The principles as enunciated by Lord Scarman in the case of ***Sidaway v. Board of Governors of Bethlehem Royal Hospitall***[19] form the corner stone of informed consent. The study suggest to respect the specific needs of different vulnerable groups to ensure that health rights are enjoyed by all within the jurisdiction of the country as per national and international guidelines. The right to freedom from violence must be protected especially in case of mentally ill and disabled. Coercive care, treatment policies and laws must be changed. In situations where populations are foreseeable oppressed, the conduct of research requires considerations that go beyond common ethical concerns and into issues of international human rights law.

Trend- Analysis of the Clinical Trial Registered in CTR India : An Empirical Study.

CTR-India yielded 879 registered trials on June 30, 2013[20]. This information on each registered trial excel spreadsheet was then exported to SPSS for

Phases	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
I	1		7	33	20	13	34	30
11	9	23	46	66	30	81	112	128
DI	25	43	99	200	111	174	191	322
1V	8	10	32	51	26	113	91	102
1/11	4	1	5	10	5	16	13	8
1J/111	4	14	12	17	13	29	22	32
M/IV		7	2	8	5	15	10	20
Post Market surveillance	11	13	23	37	35	10	26	19
NA			3	3		193	288	218

Gillick v West Norfolk area health authority (1978 QB 237), In *Freeman v Home Office* [1984 Q.B. 5241

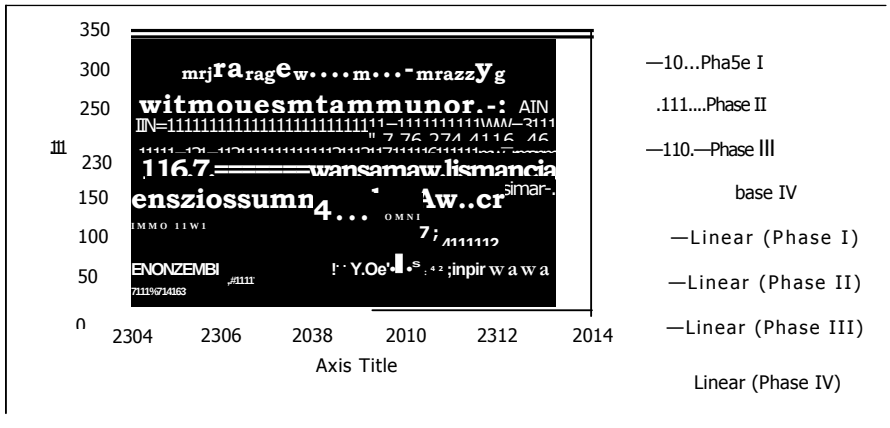
[19] 1985 I ABER 676).

20 The information on each registered trial was manually exported into an Excel spreadsheet via the copy-paste mechanism of Microsoft Office. The fields of information exported included CTR-India ID, brief study title, study status, trial location, ethics committee details, sponsor, disease condition, age group, sample size, DCGI approval and study type

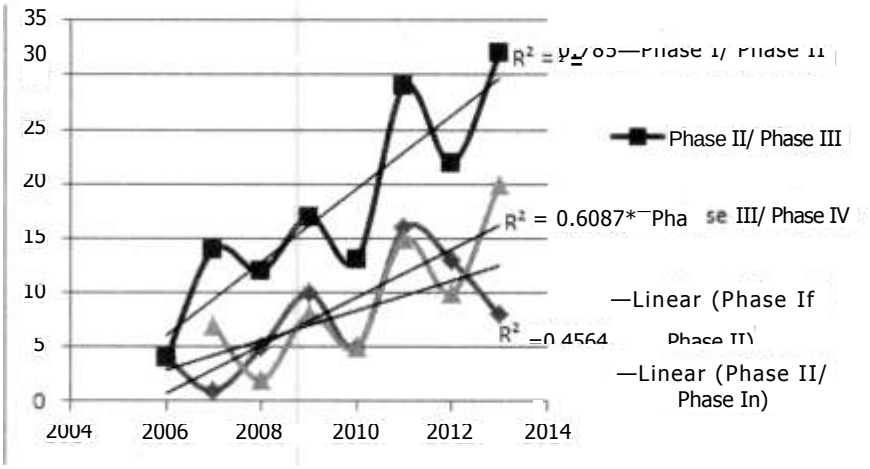
Data source Indian Journal of Medical Ethics, Clinical trial watch, from 2006 to 2012 given below. Data for June 2013 (30 June) were reported by the researcher.

Years	Phase I	Phase II	Phase III	Phase IV
2006	1	9	25	8
2007		23	43	10
2008	7	46	99	32
2009	33	66	200	51
2010	20	30	111	26
2011	13	81	174	113
2012	34	112	191	91
2013	30	128	322	102

An analysis of different phases of clinical trials is given in the table.



The graph shows that between 2006 and 2013, phase 3 trials **increased** 322 (36.6%), phase 2 clinical trials 128 (14.6%) phase 4 clinical trials 102(11.2%), and phase 1 trial to 30(3.4%) [Refer table]. The graph also indicates that between 2006and 2013, clinical trial phases 3 increased by25number to 322 number.



In terms of the phases of the trial highest of the studies is for phase i.e. 32 number in2013, lowest in 4 number 2006, for phase III/IV highest is 20 in 2013 and lowest 7 number in 2007, for phase I/II highest number 16 in 2011 and lowest number is 1 is in 2007.

Years	Phase I/ Phase II	Phase II/ Phase III	Phase III/ Phase IV
2006	4	4	
2007	1	14	7
2008	5	12	
2009	10	17	8
2010	5	13	
2011	16	29	15
2012	13	22	10
2013	8	32	20

International case law

1. A textbook example of unethical **research is the Tuskegee Study of Untreated Syphilis,** which was sponsored by the U.S. Public Health Service and lasted from 1932 to 1972,412 poor African-American men with untreated syphilis were followed and compared with 204 men free of the disease to determine the natural history of syphilis. Subjects did not provide informed consent (indeed, they were deliberately deceived); they were denied the best known treatment;

and the study was continued even after highly effective treatment became available.

2. **Coerced sterilization of HIV-positive women in Namibia-** Women in the Third World would not receive antiretroviral treatment anyway, so the investigators are simply observing what would happen to the subjects 'infants if there were no study.'

3. **Abdullahi v. Pfizern -** plaintiffs alleged that when the defendant tested Trovan (trovofloxacin, a fluoroquinolone antibiotic) for use against bacterial meningitis in Nigeria, eleven children died unnecessarily. The plaintiffs claimed that by recruiting children for testing, and failing to disclose that Trovan had been linked to life-threatening side effects in animal studies, the defendant violated a customary international law norm prohibiting involuntary medical experimentation on humans.

4. **Sosa v. Alvarez-Machain**[22] The court agreed that "non-consensual medical experimentation violates the law of nations and, therefore, the laws of the U.S." but plaintiffs had "failed to identify a source of international law that" provides a proper predicate for jurisdiction under the ATS [Alien Torts ST.

5, **Moore v. The Regents of University of California**[23]**.** The Court held that Go1de, as Moore's physician, had a legal obligation to disclose interests unrelated to Moore's health, including economic interests and research interests, which might affect his professional judgment. The question asked of the Supreme Court of California is whether defendant physician breached fiduciary duty and failed to get informed consent from patient. The court agreed with plaintiff.

6. **Re Cincinnati Radiation Litigation n** In re Cincinnati, the plaintiffs successfully argued that radiation experiments by doctors on 88 patients at the University of Cincinnati from 1960-1972 violated due process rights protected by the 14[111] Amendment to the US Constitution.

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[21] 2009 WL 214649 *at* 18

[22] 542 U.S. 692, 724-32 (2004).

[23] 1990 51 Cal. 3d 120, 793 P.2d 479, 271 Cal. Rptr. 146

[24] 874 F. SUPP. 796 (S.D. OHIO 1995)

7. **Kits V. Sherman Hospital** [25] The court held that the hospital had a duty to inform the patient of the experimental nature of the surgery, to conduct continued review of research as required by federal research regulations, and to ensure that researchers use consent forms approved by the **IRB.**

8. **Gelsinger V. University of Pennsylvania-** The lawsuit alleged that Gelsinger was not adequately informed about the risks involved in the experiment. In this case which was settled was out of court for an undisclosed amount of money.

9. **Death of Healthy Volunteer At Johns Hopkins** (2001)- Ellen Roche, died on June 2, a month after she inhaled an unapproved drug as part of a research study to examine the causes of asthma. Her lungs were destroyed, apparently by the chemical she inhaled, hexamethonium. She was 24.

10. **Grimes Y. Kennedy Krieger Institute**[26] The court also held that KKI had a duty to warn the subjects' parents of dangerous lead levels and a duty to obtain legally effective informed consent from the parents.

11. **Greenberg V. Miami Children's Hospital** (2003) The plaintiffs sued the defendants in federal court for a variety of claims including lack of informed consent, breach of fiduciary duty, fraud, conversion, and unjust enrichment. The court dismissed all of these claims except unjust enrichment, because the plaintiffs had invested considerable time and effort in helping identify the gene, and therefore deserved to share in the benefits of the discovery

12. **Vioxx Lawsuit** (2006)- More than 25 million people took Vioxx, between 1999 and 2004 to help treat long-term pain. More than 4,600 people are suing Merck, claiming that the drug caused heart attacks or strokes. The Vioxx lawsuits are significant legally because they deal with fraud and bias in the conduct of clinical trials and publication of findings

[25] 644 N.E. 2D 1214 (1995).
[26] 782 A.2D 807 (CT. OF APPEALS, MD 2001)

Indian Position/ Recent Clinical Practice

1. **A.I. Democratic Women Association v. Union of Indian** the judgment is important because the Supreme Court first time took note of the fact that there was violation of the clinical trial guidelines and a symbolic acquiescence that the Courts would not tolerate such malpractices.

2. **In Rahul Dutta v. Union of India [28] -** Justice Umanath Singh and Justice Rituraj Awasthi also noted that the Allahabad high court would consider awarding damages and came down hard on pharmaceutical companies for flouting the norms on informed consent and causing the death of subjects who were not even aware of the fact that they were being used as guinea pigs.

3. **Swasthya Adhikar Manch v Union of India" -** Apex court criticized the government for its inaction in curbing illegal clinical trials wherein the poor and destitute, particularly juveniles, tribals and dalits were being used as guinea pigs. While the matter is still being heard, one can be only hope that the Supreme Court directs the government to take concrete measures in a stipulated time period to ensure that such events do not recur.

Row over clinical trial as 254 Indian women death.

The death of 254 Indian women from modest backgrounds in the course of a 15-year US-funded clinical trial has triggered a raging debate about its ethicality. The trial was for a cervical cancer screening method and the women who died were part of a control group kept without screening to study death rates in unscreened populations. It is a well established fact that any kind of cervical screening reduces the incidence of the cancer. Yet, almost 140,000 women in the control arm of the trial were not screened. After a complaint made to it, the United States Office for Human Research Protections (OHRP) determined that the women were not given adequate information to give informed consent.[30] The trials

[27] (1998) 5 SCC 214.4

" Misc. Bench WP No. 12280 of 2010

[29] WP(C) No. 33 of 2012, March 5, 2012.

[30] The three-cluster randomized controlled trials looked for a cheap screening treatment for cervical cancer for introduction into the public health programme. The screening treatments being examined were Visual Inspection with Acetic Acid (VIA) screening, Pap smear - which is the standard of care in the west - and HPV screening

were conducted among Indian women of the lowest socioeconomic status in Mumbai slums, villages in Osmanabad in Maharashtra and in Dindigul in Tamil Nadu. These studies compared the cervical cancer death rate among 224,929 women who were offered the different types of cervical screening to that among 138,624 women ywho were offered no screening at

Supreme Court - "Why seriously affected clinical trial patients not compensated?"[32]

Taking up **PILs** seeking stringent yet transparent guidelines and norms for conduct of clinical trials in India, a bench of Justices R M Lodha and Kurian Joseph asked additional solicitor general Sidharth Luthra for details on compensation paid to patients adversely affected during clinical trial of new drugs. The health ministry had responded to allegations by NGO, Swasthya Adhikar Manch, that Indians were used as guinea pigs by foreign pharmaceutical majors for human trials of their new drugs and said of the 57,303 enrolled subjects, 39,022 completed the trials. "Serious adverse events of deaths during the clinical trials during the said period were 2,644, out of which 80 deaths were found to be attributable to the clinical trials". Luthra said kin of all 80 patients, who died because of adverse effects, were compensated by the sponsors. But the bench was focusing on the ministry's statement that "around 11,972 serious adverse events (excluding death) were reported during the period from January 1, 2005 to June 30, 2012, out of which 506 events were found to be related to clinical trials".

- For more than 12 years, as part of two massive U.S-funded studies in India, researchers tracked a large group of women for cervical cancer but didn't screen them, instead monitoring them as their cancers progressed. At least 79 of the women died.

- One study, funded by the National Cancer Institute, did not adequately inform more than 76,000 women taking part about their alternatives for getting cervical-cancer screening; and those women did not give adequate informed consent, according to the Office of Human Research Protection, part of the U.S. Department of Health and Human Services.

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[3]' Rema Nagarajan: Times of India, Lucknow Edition, April 21, 2014

32 Dhananjay Mahapatra : Times of India, Lucknow Edition 22 April 2014

- The other study, funded by the Gates Foundation, is under review by the Food and Drug Administration, according to Kristina Borror, the OHRP's director of compliance oversight. That study has raised similar concerns regarding 31,000 women who were tracked but not routinely screened or treated for cervical cancer.

- In 2003, letrozole, an anticancer drug, was tested in more than 430 young women at a dozen private clinics to find out whether it promoted ovulation. All these trials took place without regulatory approval.

- Similarly, in 2002, the pharma giant Novo Nordisk conducted multi-centre phase III clinical trials of a diabetes drug even before receiving the results of animal studies. Among other countries 550 subjects from Asia.

- In 2003-2004 the drug company Santa Biotech ran a bioequivalence study testing its version of the "clot-buster" streptokinase against the established one.

Conclusions

With the 59th report of the committee on the functioning of the CDSCO The report reveals a shockingly understaffed and abysmal infrastructure. Just 50 people handle applications for drug approval, and just 127 of 327 sanctioned posts are filled, though 1,045 are proposed. Just nine deputy and assistant drugs controllers handle 20,000 applications of various types, inspecting labs, 10,500 manufacturing units, and 600,000 sales outlets; providing information to parliament; meeting the public, attending court cases, and so on. And the CDSCO is headed by a drugs controller whose post demands nothing more than a graduate degree in pharmacy. The problem is compounded by a grossly inadequate infrastructure including data maintenance and coordination between state-level offices.

1. A comprehensive legislation is necessary to build up a system of accountability in clinical research in human experimentation to fulfill the vacuum in this area.
2. As the existing implementation is necessary, it is neither adequax nor competent, but is necessary to provide an effective implementation machinery to ensure proper health care in the country.

Recommendations

1. Consideration before giving permission to trial.

   Before approving the study in India following points requires to be considered by the Indian authorities-

   - Whether the study is terminated/ banned in any other country, If what are the reasons?
   - Whether Indian's should be benefited by the medicine.
   - Whether foreign sponsors should hire a local clinical research organization and insurance company for conducting the clinical trial in India.

2. Improve accountability through public access
3. Informed consent form should be assessed by legal /social authorities
4. Amend the law to address investigator's responsibilities
5. Legal department for the protection of vulnerable.
6. Make the ethical underpinnings of regulations more explicit.
7. Improve accountability through expanded infrastructure.
8. Ensuring legality of ethical study committee
9. Responsibility of Institutional review board/ Institutional ethics committee.
10. Designing a system of compensation. It is a threefold process.
    a. Treating and compensating for research-related injury..
    b. Treating and compensating for research-related deaths.
    c. Post-follow up
11. Ensure capacity to protect human subjects.
12. For establishment of consumer courts.
13. For criminal punishment.

Present Position in India with reference to Amendment to Drugs and Cosmetics Act under consideration- At present, medical ethics violation cases, such as negligence, are dealt with under various provisions of the Indian Penal Code (IPC). In international settings, particularly in resource-poor nations, individuals and communities participating in public health studies may be vulnerable to coercion because of their poverty

high levels of illiteracy. Strict local and inter-national REB review and monitoring is suggested. Local or foreign research should be valuable to participants and society, if ethical standards of both the host and foreign country must be upheld. These standards must be strictly followed to when conducting research in developing countries, irrespective of participants' race, socioeconomic status, or religion. The Union Health and Family Welfare Ministry is planning to add more teeth to clinical trial rules so that violators attract stringent punishment, including imprisonment, besides hefty fines in even cases where the patient is not directly impacted during the experiments with new medicines. The changes are part of the Drugs and Cosmetics Amendment Bill, 2015 which is likely to be tabled in Parliament during the upcoming monsoon session 2015. Accordingly, the government plans to introduce stringent laws for those violating these protocols. The proposed changes include a provision for a year of imprisonment if violation of rules leads to any kind of adverse impact on the patient enrolled in clinical trial. The new law would also make it mandatory for the companies conducting trial to pay fine of up to Rs 3 lakh in case of any error or violation of the protocol even if the patient is not directly impacted. In the current system often there is a conflict of interest when those conducting trials are involved in the decision-making procedure. As per the proposed rule, an independent expert committee will examine the reported adverse events and make recommendations to the DCGI, which will ultimately take a call on the quantum of punishment and compensation. Apart from clinical trials, the Bill also proposes stringent regulations for new drugs and medical devices. In fact, the changes include a separate rate chapter on medical devices, which are treated as medicines under the present law."

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" Sushmi Dey, Times News Network, **Times of India, Lucknow [Edition]Jul 5, 2015,**