CHAPTER V
LEGAL FRAMEWORK TO REGULATE CLINICAL TRIALS
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The international standards for experiments on human subjects set the foundations of ethics and legal principles to be observed by different national laws, though the legislation in each country may differ. The global standards for clinical trials were evolved from various international conventions and declarations, which set out the essential elements of good clinical practices. The issues related to experimentation on human subjects attracted the world attention after the Second World War, during the Nuremberg Trial.

This chapter is developed as two parts: Clinical trial scenario – International and Indian. The international scenario is progressed in a chronological sequence addressing various declarations, guidelines and conventions. Further, it briefly touches on the regulatory system in US and European Union before proceeding to that in India.

5.1 Clinical Trial-International Scenario–Declarations, Guidelines and Conventions

The History of Clinical Trial can be traced back to BC 562 by King Nebuchadnezzar¹. One of first documented clinical experiments was trial of inoculation as a treatment for small pox performed by Cothur Mather during the epidemic of 1721². The first international guidance on the ethics of medical research involving subjects, the Nuremberg Code³ was formulated in 1947. The Nuremberg code was not the first and the most comprehensive code on human

experimentation. It was based on various historical documents including Hippocrates oath, past experiments, and standards of ethical human experimentation. The pre war regulations prevalent in Germany on Human experimentation was a directive⁴ which was the first modern regulations by a state authority which specifically addresses the medical research and point out that medical interventions for purposes other than diagnosis, therapy, and immunization are absolutely prohibited, even though all other legal and ethical requirements for performing such interventions are fulfilled if:

- the person in question is a minor or is not fully competent on other grounds;
- the person concerned has not declared unequivocally that he consents to the intervention
- the declaration has not been made on the basis of a proper explanation of the adverse consequences that might result from the intervention⁵.

5.1.1 Nuremberg Code

The first International Guidance on the ethics of medical research involving subjects – the Nuremberg Code was formulated in 1947⁶. The Nuremberg Code was a land mark document in the history of Clinical Trials, which emphasized the need for an internationally accepted legal protection to the humanity. Pursuant to the Moscow Declaration, the Governments of the United States, France, the United Kingdom and the Union of Soviet Socialist Republics signed an

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agreement in London on 8 August 1945, which provided that there shall be established, after consultation with the Control Council for Germany, an International Military Tribunal for the trial of war criminals whose offences have no particular geographical location and the constitution, jurisdiction and functions of the International Military Tribunal was set forth in the Charter annexed to the Agreement. The agreement for the Charter is an executive agreement in the signing and the indictment and verdict must be read and construed within the limits of the Charter.

The Tribunal on the medical trials conducted by the Nazi physicians, which was already in violation of the existing German Law and the Code of Ethics of the German Medical Fraternity, had faced an issue of defining the criteria for ethical human experimentation. The Tribunal while referring to permissible medical experiments emphasized that certain basic principle must be observed in order to satisfy, moral, ethical and legal concepts. This attempt was to create a legal frame work governing the principles of human experimentation. The principles provide that

1. The voluntary consent of human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved

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as to enable him/her to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject, it should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all necessary physical and mental suffering and injury.

5. No experiment should be conducted where there is a prior reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject\textsuperscript{11}.

The Tribunal also observed that, of the ten principles which have been enumerated the judicial concern is with the requirements which are purely legal in nature or at least are so clearly related to matters legal that they assist the Tribunal in determining the criminal culpability and punishment\textsuperscript{12}.

The principles enunciated by the Nuremberg Tribunal was of great importance to clinical trials as it (i) set forth an internationally accepted guidelines for medical experimentation on human beings, though the enforceability of the same through adoption by the state laws were not established; (ii) It also focused on the attention of the world community on the possible consequences of unethical and uncontrolled human experimentation, thereby providing the impetus to nations and national and international professional association to formulate acceptable criteria\textsuperscript{13}.

The Nazi experiments were in violation of the code of ethics of German medical fraternity and the prevailing German law\textsuperscript{14}. The defendant physicians at Nuremberg claimed that medical experiments had generally been useful in furthering medical science, that in some cases the experiments alleged as criminal had increased the speed of the progress of medical science, and that in

\textsuperscript{11}Id at 181-182
\textsuperscript{12}Id at 183
\textsuperscript{13}M. C. Bassiouni, \textit{et al}, supranote 9.
\textsuperscript{14}Weinschenk,\textit{Nazis Before German Courts}, 10 INT'L LAW. 515 (1976), as cited in Supra Note 9, at p.1606,
some cases there was no other alternative for the development of medical science except to conduct experiments on human beings. This argument was rejected on the ground that in medical experiments which have been proved, the ten principles enumerated in the judgment were much more frequently honored in their breach than in their observance.\textsuperscript{15}

The trial highlighted the basic principle that the humans could not be used as experimental subjects for pure scientific investigations without regard to the therapeutic advantages. The major issue at the trial was defining the criteria of ethical human experimentation, though the Tribunal had attempted to create a legal framework governing human experimentation.

The principles of Nuremberg code are relevant in the context of HIV vaccine trials, though the code was criticized for imposing a rigid set of principles to be followed by the investigator. The adequacy of subjects consent required by these codes are uncertain as the Nuremberg Code\textsuperscript{16} provides that the consent to be voluntary without coercion and informed. These criteria could be objectionable as the results of the experiments may not be predictable, especially in the context of HIV vaccine Trials, making the procurement of a truly informed consent difficult. The nature of HIV virus, make the outcome of HIV Vaccine trial unpredictable in view of the inability of the investigator to inform the subject the potential complications of the trial due to the limited knowledge available regarding the experimental drugs. In such cases, the risk exposure which an investigator may have will be very high.

The Nuremberg Code also stipulates that\textsuperscript{17} the experiment should be so conducted as to avoid all necessary physical and mental suffering and injury, which can be argued as an unrealistic condition in view of the unpredictability of the outcome of any therapeutic technique or experimental drugs. The Code also does not discuss about the principles to be adopted for grant of compensation to

\textsuperscript{15}United States v. Karl Brandt, et al., supra note 3, at 1.
\textsuperscript{17}Id, Art. 4
be provided to the participants of a clinical trial, and also the liability of the investigator of a clinical trial.

Article 5 of the Code suggests that studies that are endangering the life of subjects are permissible, if the investigator also is a subject. This runs against natural justice, just because the investigator is ready to risk his own life, he has no right to endanger another person’s life. The Nuremberg Code was also criticized of having a close resemblance with the Guidelines of human experimentation, 1931, which was in force in Germany. There is evidence which suggest that the defendants at the trial requested that their actions be judged in the context of the 1931 guidelines which was prevailing in Germany, however such request was ignored by the prosecution. It was also criticized of using guidelines as a base document without referring to the same. Nuremberg code was not updated to meet the changes in the scenario of Clinical research, and the code in its entirety was not accepted as a standard in clinical research.

5.1.2 Universal Declaration of Human Rights

Universal Declaration of Human Rights is a declaration adopted by the United Nations General Assembly on 10 December 1948. It contains thirty articles which sets effective recognition and observation of human rights and a fundamental constitutive document of United Nations and has created a new era in human history. The Declaration promulgates the right to life, liberty and security of person a perect embodies in it and also emphasize that no one shall be subject to torture, or to cruel or inhuman or degrading treatment or punishment.

The declaration does not define the term torture. Human experimentation without informed consent, and the consequences of which may not be foreseen by any

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19 Id.
21 Id.
investigator may amount to violation of the Article 3 and Article 5 of the Universal Declaration of Human Rights, the recognition of inherent dignity, equal rights of all members of human fraternity. To give the Declaration legal as well as moral force, in 1966, the United Nations General Assembly adopted the International Covenant on Civil and Political Rights, which states No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation. Human rights place a duty on the state and on healthcare providers to comply with minimum standards. Medical ethics place a duty on individual doctors to comply with parallel standards. Both are complementary, and use of the two together maximizes the protection available to the vulnerable patient.\textsuperscript{22}

The Universal Declaration of Human Rights upholds the rights, dignity, and freedom of individuals and the need to protect people from "arbitrary interference. However the international legal standard does not guide physicians in the manner of obtaining the consent of their subjects. Rather, human experimentation is guided only by a host of informal guidelines, and individual nations lack the capacity to punish physicians for human experimentation in violation of those guidelines.\textsuperscript{23}

The Universal Declaration of Human Rights (UDHR), while establishing the concept of "bodily integrity," lacks the specificity necessary to provide a link to human experimentation. The UDHR provides that "Everyone has the right to life, liberty and security of person\textsuperscript{24} and that "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment\textsuperscript{25}, which together are known as the right to bodily integrity. The International Covenant on Civil and


\textsuperscript{24} Universal Human Rights Declaration, United Nations General Assembly, supra note 20.

\textsuperscript{25} Id, Art.5.
Political Rights also similarly provides the right to bodily integrity\textsuperscript{26}. The Health services depend absolutely on the public’s confidence and trust compromising on respect for autonomy would undermine this basic issue. Although the Universal Declaration of Human Rights was intended to be nonbinding, through time its various provisions have become so respected by states that it can now be said to be customary International Law\textsuperscript{27}.

5.1.3 Helsinki Declaration

- In September, 1961, the Ethical Committee of the World Medical Association formulated its provisional conclusions from its study of experiments involving humans and presented them in a Draft Code of Ethics on Human Experimentation to the General Assembly of the World Medical Association, the final version of which was accepted at the meeting of the World Medical Association at Helsinki in 1964 and is known as the Code of Ethics on Human Experimentation of the World Medical Association/ Helsinki Declaration\textsuperscript{28}. The “Helsinki Declaration” (1964), thereafter was revised many times, the latest being in 2008\textsuperscript{29} which spells

out a set of ethical guidelines for physicians and other participants in medical research. Even before the Helsinki Declaration, in 1954, the World Medical Association, at its Eighth General Assembly in Rome, adopted the Principles for Those in Research and Experimentation. These five basic principles emphasize that:

(1) Scientific and moral aspects of experimentation, experimentation should be conducted only in a scientific manner by qualified individuals and there should be strict adherence to the respect for the individual’s rights;

(2) The researcher bears primary responsibility in human experimentation and not the willingness of the research participant;

(3) Informed consent must be obtained in writing for experimentation on both sick and healthy patients and

(4) Publication of the first results of experimentation should be done with prudence and discretion to avoid the detrimental effects of premature and unjustified statements

(5) Experimentation on sick subjects requires consent of his own or of his next kin.\(^{30}\)

The Declaration of Helsinki is a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles\(^{31}\). Clinical Trial is an area which involves professionals from different areas; however it is quite possible that other professional bodies can have different views on the principles adopted by WMA. The Original Declaration of Helsinki has its ancestry in the Nuremberg Code. The Declaration highlights the duty of the physician as to promote and safeguard the health of patients, including those who are involved in medical research and the

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\(^{31}\) Id
physician’s knowledge and conscience are dedicated to the fulfillment of this duty. Further it also mentions that in medical research involving human beings, the well being of individual research subject must take precedence over all other interests.

The Declaration has adopted the ten principles stated in the Nuremberg Code and the Declaration of Geneva which describes the physician’s ethical duties. The fourth revision of Helsinki declaration provides that, in any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists. The issue of placebo control, high lights the need for delicate consideration to balance ethical tensions, which often exists between research which seeks to obtain answers as efficiently as possible and the well being of the participant of the research occurred in the context of rising disquiet about the use of placebo controls in the studies of materno-fetal HIV Transmission.

With regard to the standard of care, the Declaration of Helsinki contends that the best known methods of treatment, diagnosis, and prevention should be provided. After contentious debate, the WMA upheld this position at its 2000 Edinburgh meeting, adopting essentially the same principle, with the minor modification of changing “best proven method” to “best current method”. It mentions that the benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic method.

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32 *Id.*, Arts. 3, 5, 
33 *Id* Art. 6


35 Humphrey, *supra note 27*, at
36 DECLARATION OF HELSINKI, *supra note 29.*
However later it is clarified stating that ‘WMA reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general, this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, in situations where for compelling and scientifically sound methodological reasons, its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method’\textsuperscript{37}.

Paragraph 29 of the Declaration of Helsinki has been widely interpreted to mean that participants in the control arm of a trial are entitled to a “universal” standard of care\textsuperscript{38}. The Helsinki declaration provided for review, guidance and approval of ethics committee and also mandated approval of ethics committee under certain circumstances, where the informed consent cannot be obtained. The declaration contains a number of contradictory recommendations. For instance, in Article 4 the Declaration claims that it only “binds the physician”, but then proceeds in Article 30 to delineate ethical obligations of authors, editors, and publishers who are frequently not physicians. Similarly, the Declaration of Helsinki argues that physicians’ primary consideration must be to promote the health of patients in Article 3. However, Article 11 states that physicians who take part in medical research need “to protect the life, health, and dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects”. Such protection—eg, self-determination and privacy—can conflict with promoting the health of patients\textsuperscript{39}.

\textsuperscript{37}Humphrey, supra note 27. Amendment in the form of a footnote to Paragraph 29, approved by the WMA General Assembly, Washington DC, 2002.


The revised Declaration of Helsinki⁴⁰, states that every clinical trial must be registered in a publicly accessible database before recruitment of the first subject, which has also contributed to the establishment of clinical trial registries and making the data available to the public, thereby assisting the physicians in taking appropriate treatment decisions. The declaration mandates that, the protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study⁴¹. These aspects are not covered in ICH guidelines and are critical information regarding the research and will assist in preventing frauds or manipulations.

Further, proper disclosure regarding the incentives, treatment and compensation for the subjects, will bring clarity and will be in the best interests of the participants. The declaration also mentions that, in clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions, leaving lot of discretion to the competent authorities of the national regulatory authorities to prescribe post trial access to treatment and other provisions in accordance with the local laws and the practices. The declaration also insists for publication of results of clinical trial, establishment of Clinical Trial Registries and that the research should benefit and be responsive to health needs of, populations in which research is done, and restricted use of placebo controls even where there is no practical access to costly drugs in developing countries, which all are not stipulated in ICH guidelines, thereby making it a more comprehensive and important document related to human research.

The impact of the declaration on the society was considerable. The Society has a clear interest in the implementation of the Declaration not least because the

⁴¹Ibid, Art.22,
history of human experimentation cannot be recounted without reference to the abuses described\textsuperscript{42}.

5.1.4 Belmont Report

The Belmont report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research was created by the National Commission for protection of Human subjects of Bio Medical and Behavioural Research, the first public national body to shape bio ethics policy in the United States\textsuperscript{43} formed after the Tuskegee Syphilis study\textsuperscript{44}. The Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department’s policy. The Department requests public comment on this recommendation\textsuperscript{45}. Based on the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974-1978), the Department of Health and Human Services (HHS) revised and expanded its regulations for the protection of human subjects 45 CFR part 46 in the late 1970’s and early 1980’s. In 1991, 14 other Federal departments and agencies joined HHS in adopting a uniform set of rules for the protection of human subjects, identical to subpart A of 45 CFR part 46 of the Health and Human Services regulations\textsuperscript{46}.

Belmont Report distilled the Nuremberg Code and Declaration of Helsinki into three overreaching basic ethical principles; autonomy, beneficence and justice, as its core theory. The first and foremost is respect for persons also known as autonomy. This is reflected in an individual’s decision to accept or refuse

\textsuperscript{43} Title II, The National Research Act, 1974
\textsuperscript{44} An infamous clinical study conducted by U.S Public Health service for treatment of syphilis on blacks, available at http://www.cdc.gov/tuskegee/timeline.htm, (Last visited on November 12, 2014).
participation in research. This is followed by beneficence, defined as benefiting the individual or human kind while minimizing unnecessary risks. Finally the research must be just, is it must be fair and equitable neither forgetting nor benefiting one group of individuals over other. The application of this principle requires that the moral requirements of fair procedure and outcomes in selection of research subjects are to be followed especially when vulnerable subjects are involved in the research, in view of their recurrently compromised capacity to free consent.

The report emphasize the application of three requirements viz, informed consent, amount of risks as well as benefits and selection of the research subjects. In a study conducted based on the interviews with the community-based participatory researchers, some of the interviewees were satisfied with the scope of ethical considerations covered by the Belmont principles, which was partly due to the meaning of the principles being sufficiently abstract to allow for flexible interpretation, or having been schooled in the Belmont principles and, consequently, unable to think of other principles. While the level of abstraction represented a benefit for some of the interviewees, others advocated for greater specification of the current principles. There was also a call to clarify the language in order to make the meaning of the principles more accessible and less confusing.

Belmont report was criticized for several reasons and considered as a conceptually flawed ethical theory. It was argued that Belmont report made a philosophical error in its attempt to derive moral requirement for informed consent from the principle of respect for persons, as it was argued as a

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47 R.D. Toto and M. J McPhaul, Clinical Research from Proposal to Implementation
49 Id.
misguided conception of autonomy. The respect for autonomy can conflict with other ethical considerations, can have multiple meanings, and there was no substantive guidance towards making these decisions.

The Report fails to harmonize beneficence with respect for persons. The Report notes that there are differences of opinion about the just distribution of burdens and benefits suggesting that benefits to others, if sufficiently great, could outweigh harm to the individual subject. The Belmont Report also emphasizes the importance of recognizing the boundaries between practice and research. In practice, the Belmont Report demands that human research involves approval by an ethics committee, voluntary informed consent, and researcher judgment with respect to risks. Though the Belmont Report was never endorsed officially, it has served as an ethical standard for Institutional Review Boards (IRBs), which require researchers to submit their research proposals for their approval. The Report had tremendous practical significance for the monitoring of research on human subjects.

5.1.5 International Ethical Guidelines for Bio Medical Research involving Human Subjects

In 1982, World Health Organization (WHO) and CIOMS issued the Proposed “International Guidelines for Bio Medical Research involving Human Subjects” and “International Ethical Guidelines for Bio Medical Research involving Human Subject” (1993). CIOMS set out, in cooperation with WHO, to prepare guidelines “to indicate how the ethical principles that should guide the conduct of biomedical research involving human subjects, as set forth in the Declaration of Helsinki, could be effectively applied, particularly in developing countries, given their


socioeconomic circumstances, laws and regulations, and executive and administrative arrangements.53

The CIOMS guidelines address mainly ethical justification and scientific validity of research; requirements for ethical review and informed consent; consideration of vulnerability of individuals, groups, communities, and populations; women as research subjects; equity regarding burdens and benefits; choice of control in clinical trials; confidentiality; compensation for injury; strengthening of national or local capacity for ethical review. The CIOMS Guidelines provide that the Independent Ethical Review Committee shall have the authority to approve or reject research protocols54.

After 1993, ethical issues arose for which the CIOMS Guidelines had no specific provision. They related mainly to controlled clinical trials, with external sponsors and investigators, carried out in low-resource countries and to the use of comparators other than an established effective intervention. The issue in question was the perceived need in those countries for low-cost, technologically appropriate, public-health solutions, and in particular for HIV/AIDS treatment drugs or vaccines that poorer countries could afford. The Guideline 11 was redrafted to reduce the conflict and the commentary of the Guideline reflects the un-resolvable conflict on the issue55. Further, leaving every aspects to local decision making can adversely affect the participants of countries where the legal system and enforceability is not very strong, which may eventually lead to further exploitation.

The CIOMS guidelines addresses the complex issues involving HIV vaccine clinical trials which includes, the individual informed consent, research involving vulnerable persons, obligations of sponsors and investigators in obtaining

54 Id, Guidelines no3,
55 Id
informed consent, right of the injured subject to compensation and treatment, safeguarding confidentiality etc. For research involving persons who are unable to consent, or whose capacity to make an informed choice may not fully meet the standard of informed consent, ethical review committees must distinguish between intervention risks that do not exceed those associated with routine medical or psychological examination of such persons and risks in excess of those. When the risks of such interventions do not exceed those associated with routine medical or psychological examination of such persons, there is no requirement for special substantive or procedural protective measures apart from those generally required for all research involving members of the particular class of persons.

When the risks are in excess of those, the ethical review committee must find:

1) that the research is designed to be responsive to the disease affecting the prospective subjects or to conditions to which they are particularly susceptible;

2) that the risks of the research interventions are only slightly greater than those associated with routine medical or psychological examination of such persons for the condition or set of clinical circumstances under investigation;

3) that the objective of the research is sufficiently important to justify exposure of the subjects to the increased risk; and

4) that the interventions are reasonably commensurate with the clinical interventions that the subjects have experienced or may be expected to experience in relation to the condition under investigation.\(^{56}\)

Ethical Committee was given lot of discretion with regard to the decisions on person who are incapable of providing informed consent. However the issue is, there may not be any uniformity on functioning of the Ethics Committee and to

\(^{56}\) Id, at p.50,
what extent justice can be expected from the Ethics Committee is a real challenge for protecting the subjects involved in clinical research.

The commentary on Guideline 3 of CIOMS, suggests that the committees in the host country have a special responsibility to determine whether the objectives of the research are responsive to the health needs and priorities of that country. When a sponsor or investigator in one country proposes to carry out research in another, the ethical review committees in the two countries may, by agreement, undertake to review different aspects of the research protocol. The ethical review committee in the host country can be expected to have greater competence for reviewing the detailed plans for compliance, in view of its better understanding of the cultural and moral values of the population in which it is proposed to conduct the research. In case of research in host countries with inadequate capacity for independent ethical review, full review by the ethical review committee in the external sponsoring country or international agency is necessary\(^{57}\). However, who will judge the competence of the ethical review committee is the real issue. Many times, it is possible that the incompetency of the host countries ethical review committee will be taken as an advantage by the sponsors or developing countries.

Current International Guidelines (e.g., the Declaration of Helsinki, the CIOMS Guidelines, and the UNAIDS Ethical Considerations) include provisions that require researchers from High and Middle income countries (HMIC) to negotiate with the host country collaborators about the conditions under which the research will be conducted, including what benefits are expected to accrue to the host communities, prior to the start of the research. They also include provisions about the assurance of on-going access to any intervention demonstrated to be effective through the course of the study. These assurances are commonly known as "post-trial obligations." The guidelines also state that, in the course of research activities, opportunities must be found to enhance the capacity of the

\(^{57}\text{Id}\)
Low Middle Income Countries (LMIC) collaborators and their institutions to conduct and be full partners in research\textsuperscript{58}.

These obligations will have financial implications and could be burdensome for private industries whose interest is increasing in clinical research; as such fulfillment of these post trial obligations in a meaningful manner can make significant changes in the developing countries, hosting clinical trials. Guideline 10 of CIOMS guidelines\textsuperscript{59} mentions on responsiveness which cast an obligation on the sponsor and investigator to ensure that the research is responsive to the health needs of the population or the community and any intervention or product developed shall be reasonably available to the community. However what is reasonable is always subjective and there could be vast difference in the yardsticks applied in the host country and home country.

The CIOMS Guidelines regulates how research funded by developed countries to perform experiments with subjects in developing nations. The Guideline requires that the research subjects from developing communities, should not be used in research that could be carried out reasonably well with subjects from developed countries. The research should be responsive to the health needs and priorities of the host country and meets the requisite ethical standards\textsuperscript{60}.

Responsiveness is aimed at preventing exploitation as the trial sponsors are expected to identify the extent of benefit that makes the host community fair ie fair amount of benefit and the fairness depends on to what extent the benefits the host community may receive. In case of trials which are a failure at the initial stages and an improved version of the same product developed based on the studies conducted initially, whether the host community who participated initially in the trial are entitled for any benefits is not very clear.


\textsuperscript{59} L. H. Lund and K. Swedberg, \textit{supra} note52.

\textsuperscript{60}Id, Guideline no3.
There is a need for a pre trial agreement between the regulatory authorities of the host country and home country to resolve many unresolved issues related to benefit sharing and post trial follow up obligations and this will be beneficial to the developing countries. Many times, the international guidelines issued lacks stringent enforcement measures and may be the outcome of a compromise. The developing countries may not be able to effectively negotiate terms and conditions which are beneficial to them. The Guidelines also requires that the externally funded research should obtain approval from ethical review committees in both the home and host states.

The CIOMS Guidelines has influenced the research, investigators and the ethical committees that review the same, however non binding nature of these guidelines and lack of enforcement mechanisms, poses a challenge to implementation of a favorable change for experiments on human subjects. The recent revision of the Council for International Organizations of Medical Sciences (CIOMS) guidelines provides the clearest statement of the need for a scientifically valid reason for using a lower standard of care.

5.1.6 Convention on Human Rights and Biomedicine, or “the Oviedo Convention

The member states of the Council of Europe in 1999 entered into the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, otherwise known as the Convention on Human Rights and Biomedicine, or “the Oviedo Convention”, a comprehensive multilateral treaty addressing various aspects of bioethics. The Oviedo Convention was ratified by many European States and the States having ratified it are obliged to bring the national laws in conformity with the principles of the treaty.

The Oviedo Convention has adopted a comprehensive approach to bio ethics and adopted a minimum common standard which are obliged to be introduced
into the national legislation of the countries ratifying the convention. It is a broad frame work instrument which is intended to be developed in future by introducing additional protocol on specific issues. The convention affirms the primacy of human being\textsuperscript{61} and equitable access to health care, stating that the interest and welfare of the human being shall prevail over the sole interest of the society or the science. This is highly relevant in the context of HIV vaccine trials, where the issues of placebo controlled studies are done.

The individual participant is at a higher risk in HIV vaccine trials, due to the complexity of the disease.\textsuperscript{62} Article 4 of the Convention mentions the professional standards of doctors and health care professionals generally whose interactions in clinical settings can have profound effect and social workers who are members of team involving in the decision making process and carrying out interventions. The convention also states that when the research does not have the potential to produce results of direct benefits to the health of the person concerned, such research may be authorized, subject to the additional condition that, the research entails only minimal risk and minimal burden for the individual concerned\textsuperscript{62}.

The participants who belong to the vulnerable group, especially sex workers will have a higher risk and the issue of minimal burden cannot be complied in the event of participant getting HIV infected during the course of trial. Though it can be a matter of interpretation, the binding nature of the instrument as it was ratified by many of the European countries, can create compliance issues for HIV Vaccine Trials.


\textsuperscript{62} Id, Art.17
The Convention so far is the only legally-binding and enforceable international text in the area of bioethics. The Oviedo Convention does not use the term bioethics. Although the word bioethics was first to be included in its title, eventually it was repelled from the document. The Convention mandates the protection of the dignity and identity of all human beings without any discrimination and stresses the supremacy of the interests and welfare of the human being over the sole interest of society and science, which reflects the most basic concepts of the Convention. Because of the binding nature of the convention, it has become a remarkable provision in the field of human research. It also specifies the obligation to obtain free and informed consent to any medical intervention from persons concerned. It addresses the issue of "scientific research" and enshrines the principle of freedom of research. But it also states several conditions that have to be met for research to take place, which includes the need to obtain the potential research subject's free and informed consent, approval of the project by a competent body, freedom of the participant to withdraw from the research at any time. It also mentions that the risk that may have incurred by a participant should not be proportionate to the benefit from the research. This cannot not be guaranteed in an HIV vaccine clinical trial, in view of the risks involved and the complexities associated with the virus. The Convention also mandates for a multidisciplinary ethical committee, which was a progressive step in this regard. Article 17 lay down general rules, as well as special provisions regarding persons not able to consent to research.

5.1.7 Universal Declaration on Bioethics and Human Rights (2005)

Identifying and working on bio ethical issues is one of the complex tasks and UNESCO’s Universal Declaration on Bioethics and Human Rights (UDBHR) are irreplaceable for a comprehensive study of research on human beings. The most

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64 L. H. Lund and K. Swedberg, Chapter I, Art.1 and 2, supra note 52.

65 L. H. Lund and K. Swedberg Chapter II, Chapter V, supra note 52.

66 Id.
significant aims of the declaration are to provide a universal frame work of principles and procedures to guide states in the formulation of their legislation, policies or other instruments in the field of Bio ethics, to guide actions of individuals, groups, communities, institutions, corporations public and private.

The Declaration recognizes the principle of autonomy and individual responsibility\(^{67}\), issues related to consent, persons without the capacity to consent\(^{68}\), respect for human vulnerability, and personal integrity\(^{69}\), privacy and confidentiality\(^{70}\) and also the aspect of individual responsibility which is very important in HIV Vaccine clinical trials as a trial participant can cause harm to others by non compliance with the study requirements and the obligations undertaken as a participant. The declaration also mandates that the direct and indirect benefits to patients, research participants and other affected individuals should be maximized and any possible harm to such individuals to be minimized\(^{71}\).

However the issue is whether the research participants, sponsors or investigators are in a position to foresee the potential harm that may be caused to a participant in a clinical trial, which may vary depending on various factors. The convention does not address the issue of state responsibility or the community responsibility at an international level to take care of the research participants who is suffering from the consequences of a clinical trial.

The declaration mandates that the consent to be free, express, the prior, and informed consent of the person concerned, should be based on adequate information. The consent should, where appropriate, be express and may be withdrawn by the person concerned at any time and for any reason without


\(^{68}\) Id, Art 6 and 7 ,

\(^{69}\) Id Art 8,

\(^{70}\) Id Art 9,

\(^{71}\) Id Art.4,
disadvantage or prejudice\textsuperscript{72}. Though the Declaration addresses the issue of capacity to consent in accordance with the domestic law, the more crucial issue of the capabilities of the individual to take informed decision are not addressed. In such cases where the individual does not have any capability to take informed decisions, the state intervention in a manner to protect the individual interests ought to be available. It also refers the principle of solidarity\textsuperscript{73}. The principle of solidarity implies that researchers in medical sciences can appeal to the solidarity of individuals, because these individuals have benefitted from earlier research and will possibly benefit from future research. However, individuals still have the right to refuse participation. Their duty consists in that they should at least consider such appeal and substantiate a refusal with valid arguments\textsuperscript{74}. Sharing of benefits resulting from any scientific research and development\textsuperscript{75} and the principle of social responsibility and health\textsuperscript{76} which aims to provide quality health care and essential medicines especially for women and children, adequate nutrition and water, reduction of poverty and illiteracy, improvement of living conditions and the environment. Finally, the Declaration anchors the bioethical principles firmly in the rules governing human dignity, human rights and fundamental freedoms.

It also recognizes the importance of freedom of scientific research and the benefits derived from scientific and technological developments while stressing the need for such research and developments to occur within the framework of ethical principles set out in this Declaration and to respect human dignity, human rights and fundamental freedoms\textsuperscript{77}. This is one of the first international documents which acted as a frame work of principles and procedures to guide states in enacting legislations. The UDBHR also envisages the co-operation of International Bioethics Committee (IBC) in Implementing Universal Principles at

\textsuperscript{72}Id Arts 5 and 6
\textsuperscript{73}Id
\textsuperscript{74}Id
\textsuperscript{75}C. H. Lund and K. Swedberg, Art. 15, supranote 52.
\textsuperscript{76}Id, Art.14,
\textsuperscript{77}Id, Art 2,ibid
the National Level, a multidisciplinary, multicultural body of experts with a global scope, mandated to elaborate the principles contained in the UDBHR, with an aim to facilitate their implementation at country level.

5.1.8 The Joint United Nations Programme on HIV and AIDS, or UNAIDS

Established in 1994 by a resolution\textsuperscript{78} of the UN Economic and Social Council and launched in January 1996, UNAIDS is guided by a Programme Coordinating Board with representatives of 22 governments from all geographic regions, the UNAIDS Cosponsors, and five representatives of nongovernmental organizations (NGOs), including associations of people living with HIV/AIDS\textsuperscript{79}.

In September, 1997, the Joint United Nations Programme on HIV/AIDS (UNAIDS) embarked on a process of international consultation; its purpose was further to define the important ethical issues and to formulate guidance that might facilitate the ethical design and conduct of HIV vaccine trials in international contexts\textsuperscript{80}. Representatives from developed and developing countries began to identify the major ethical challenges that needed to be confronted in relation to international HIV vaccine research. Brazil, Thailand, Uganda, the three countries representing different geographical regions were invited to host these

\textsuperscript{79} Id, Art 2, ibid
workshops in April and May, 1998 in view of their previous involvement in HIV vaccine trials, their familiarity with the relevant scientific and social issues, and their imminent need to develop greater familiarity with the ethical implications of vaccine research\textsuperscript{81}. The major outcome of the consultation process includes:

(a) the disapproval of the historic practice of testing pharmaceutical products in developing countries without ensuring access for residents of the host country to successful products resulting from the research. Agreement was not reached on how accessibility could be ensured, or on how broadly a new product should be made available

(b) the use of Developing Country and Developed Country terminology were inadequate and in place of the developing/developed terminology, each region described the factors that are likely to influence the degree of vulnerability of the prospective subject population to exploitation or harm

(c) Urgency for a vaccine development versus protection of human subjects

(d) Conditions that should be fulfilled prior to conducting HIV vaccine trials in developing countries might include the following:

(i) The vaccine is expected to be effective against a strain of HIV virus that is a relevant public health problem in the host country

(ii) The host country has, or with assistance can develop, adequate scientific capability and administrative infrastructure for the successful conduct of the proposed research

(iii) The host country has, or with assistance can develop, the capability to conduct scientific and ethical review

(iv) Community members, policy makers, ethicists and researchers in the host country have determined that their residents will be adequately protected from harm or exploitation, and that the vaccine development

\textsuperscript{81} Id.
programme is responsive to the health needs and priorities in their country.

(e) Contributors agreed that “high quality” HIV prevention counseling must be provided for all trial participants. Exactly what information should be conveyed through what specific methods was not agreed upon.

(f) The most contentious issue arising from the consultation process was whether there is an ethical imperative for participants in an HIV vaccine trial to be provided with treatment, should they become infected during the course of the trial. Workshop participants within each region reached a consensus on the question of treatment, but the consensus reached was different for each region. Positions ranged from providing the “best proven” treatment, to providing the level of treatment that is readily available within the host country.

(g) Another perspective arises from the framework of global social justice. This argument points to the disparity in economic resources that exists between countries. HIV preventive vaccine trials will likely be funded by sponsors from countries with greater wealth and better health care than the host country populations in which they are eventually tested. In many of the potential host countries, there is no treatment available to the general population. In addition, sponsor companies are likely to profit from the eventual sale of preventive HIV vaccines. Providing treatment to those infected with HIV during vaccine trials in developing countries would be a step towards addressing an ethical obligation for international researchers to contribute towards equality of resources.\textsuperscript{82}

UNAIDS aims at a co-ordinate and comprehensive action plan for global action against AIDS. The United Nations General Assembly has adopted a Declaration of Commitment on the Human Immunodeficiency Virus/Acquired Immuno Deficiency Syndrome (HIV/AIDS) as a matter of urgency, to review and address the problem of HIV/AIDS in all its aspects, as well as to secure a global,

\textsuperscript{82}Id.
commitment to enhancing coordination and intensification of national, regional and international efforts to combat it in a comprehensive manner\textsuperscript{83}. The Declaration also recognizes that the effective prevention, care and treatment strategies will require behavioural changes and increased availability of, and non-discriminatory access to, vaccines, drugs, including anti-retroviral therapy, as well as increased research and development\textsuperscript{84}. Further, it mentions about increase in investment and to accelerate research on the development of HIV vaccines, support and encourage increased national and international investment in HIV/AIDS-related research and development, and in particular, appropriate, safe and affordable HIV vaccines and their delivery and create a conducive environment for research and ensure that, it is based on the highest ethical standards\textsuperscript{85}.

After the controversies and debates about trials of tenofovir for HIV pre-exposure prophylaxis, UNAIDS initiated a year-long process to promote effective partnerships between researchers and civil society in HIV prevention trials, culminating in the ‘Creating effective partnerships for HIV prevention trials’ consultation in June 2005\textsuperscript{86}. The Good Participatory Practice guidelines (GPP) were born out of a recommendation from the UNAIDS, Creating Effective Partnerships in Research process in 2005, developed by UNAIDS and AVAC and are primarily written for Trial funders, sponsors, and implementers include investigators, research staff, and all others involved in designing, financing, and executing biomedical HIV prevention trials. The first GPP guidelines was published in 2007 and is a comprehensive guidance on the participatory conduct

\textsuperscript{84}/id, Para 23.
\textsuperscript{85}/id, Para 70.
of biomedical HIV prevention trials and was not intended to provide guidance on all scientific and ethical aspects of these trials.\textsuperscript{87}

The guiding principles of GPP in biomedical HIV prevention trials are

- Respect
- Mutual understanding
- Integrity
- Transparency
- Accountability
- Community stake holder autonomy.\textsuperscript{88}

Trial sponsors and implementers are ethically obligated to ensure that participants who acquire HIV during trial participation have access to clinical evaluation, and stage-appropriate HIV care and treatment. This issue is often at the forefront of community stakeholder concerns. Therefore, how access to HIV care and treatment is negotiated with relevant stakeholders and how it is provided to trial participants are likely to have a significant influence on community stakeholder perceptions of a trial. In GPP guidelines, the preferred term is community stakeholders rather than community and refers to both individuals and groups representing the participants of Clinical Trials\textsuperscript{89}.

\textbf{5.1.9 International Conference on Harmonisation of Technical Requirements for Registration of pharmaceuticals for Human Use}

The appropriate expert group of International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has developed ICH Harmonized Tripartite guidelines, guideline for Good Clinical Practice E6(R1), subject to consultation by the regulatory parties, in accordance with the ICH Process.


\textsuperscript{88} Id.

\textsuperscript{89} Id.
ICH initiative is an interregional venture covering 17 high income countries. The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. The ICH guidelines are part of the national legislations of European Union and USA as such its enforceability and acceptability are more unlike other legislations. The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.90

ICH GCP guidelines defines Clinical Trial91 as any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

This definition is clearly distinct from the definition adopted by World Health Organization which describes Clinical Trial as "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.92 The

91 Id., Cl. 1.12
definition as mentioned in ICH GCP is more focused; however, the WHO definition of Clinical trial is more broad and capable of including any intervention which is capable of having an impact on the health outcome of the trial subjects.

The Guidelines defines vulnerable subjects and mentions that special attention needs to be given by the Institutional review Board/ Independent Ethics Committee, in case of vulnerable subjects. Hence it is open for the Institutional Review Board / Ethics Committee to take appropriate decisions based on the facts and circumstances of each case and no specific guidelines were given in this regard.

The ICH guidelines has not addressed the aspects of waiver of informed consent, or any class of activities where the approval of Institutional review board/ Ethics Committee approval can be waived. As such informed consent and approval of Institutional review Board / Ethics Committee are pre requisites for any trials where the ICH guidelines are adopted or applicable. The ICH GCP guideline (E6, “Good Clinical Practice: consolidated guideline”) deals with the planning, conduct, monitoring and reporting of clinical trials. Its object is to facilitate the mutual acceptance of clinical trial data in ICH countries.

The ICH GCP guidelines are used by non-ICH countries to develop their own GCP guidelines, but they do not address country specific issues. ICH GCP does not address the access of benefits of the research to the Community or how the benefits and burdens are shared. It does not address many issues like criteria for a fair selection of subjects, or for the protection of poor or marginalized from exploitation, rather suggest such criteria to be included in the research

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\(^{93}\) Council of Europe, The Committee on Bioethics, supra note 63, Cl. 1.61,

\(^{94}\) Id Cl.3.1.1.


protocol. ICH guidelines are not revised for more than 15 years and are too broad and capable for a liberal interpretation.

It is better to have clear definitions and criteria to be specific, which may give less room for local interpretation, as the clinical research are conducted in a global environment. Its enforceability depends on its incorporation in the national legislation. Though it ensures confidentiality of the identity of the subjects, it is silent on the period of retention of records, and tenure of the confidentiality obligations and refers to the regulatory requirements on such areas where it is silent.

5.1.10 WHO GCP Guidelines and other Initiatives

In 1995, WHO issued Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products, with an object to set globally applicable standards for the conduct of such biomedical research on human subjects. The WHO–GCP and ICH-GCP are similar in its principles. The WHO–GCP guidelines were issued as guidance for researchers, ethics committee and regulatory agencies of the countries where no further guidance existed. The ICH-GCP was a harmonized guideline for the ICH region countries, for adaptation as a regulatory standard and to meet the Technical Requirements for registration of pharmaceuticals for human use and is adopted by European Union.

WHO has issued a Hand Book for Good Clinical Research Practice in 2002 as an adjunct to WHO’s “Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products” (1995), and is intended to assist national regulatory authorities, sponsors, investigators and ethics committees in implementing GCP for industry sponsored, government-sponsored, institution-sponsored, or investigator-initiated clinical research.

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The WHO GCP guidelines are addressed to investigators, ethics review committees, pharmaceutical manufacturers and other sponsors of research, monitors, statisticians and drug regulatory authorities. The WHO GCP principle 1, insists for research to be scientifically sound and adhere to the ethical principles which are having their origin in the declaration of Helsinki. Principle 3 of WHO GCP mentions that before research involving humans is initiated, the foreseeable risks and any anticipated benefits for individual trial subject and society to be identified. It is imperative that the social risk faced by the participants should be identified and they are required to be safeguarded against all such risks, which is required for the success of vaccine research.

This may be seen in the context of the issue, whether or not an infection acquired by vaccine trial participants during the course of the trial can reasonably be considered a trial related injury, that ought to be subject to compensation (in the form of access to good quality AIDS treatments, including antiretrovirals). It is also to be noted that some trial participants would become infected during the course of such trials due to a phenomenon known as the therapeutic misconception, that is, the mistaken idea that they have received a working HIV vaccine offering some or complete protection.

There are arguments against and favour of treating the above as trial related injuries on the basis of the risk behaviour of the participants compared to the rest of the populations from where they were recruited. However unless there is

100C. Weijer & G. LeBlanc, Revisiting the ethics of HIV prevention research in developing countries, 10, Department of Bioethics, Dalhousie University, 2005, available at: http://swgpp.pbworks.com/w/file/1_Revisiting+the+ethics+of+HIV+prevention+research+in+developing+countries.doc.doc (Last visited on March 12, 2014).
clarity with regard to the scope of trial related injury in HIV Vaccine Trials, it is doubtful whether the participants will be able to claim the benefits of these principles. If contacting HIV during or after the trial is a trial related injury, the foreseeable risk for a participant of clinical trial will be very high.

Principle 4 of the WHO GCP mentions that, although the benefit of the results of the trial to science and society should be taken into account, the most important considerations are those related to the rights, safety, and well-being of the trial subjects. The participants of HIV Vaccine trials are vulnerable groups, and as such with a high risk behaviour, the manner in which the safety and well being to be ensured is a relevant fact and whether it should go to the extent of educating them for reducing their risk behaviour and the impact of such safety measures on the outcome of the vaccine trial needs to be considered. The enforcement of the rights, safety and well being of the participants could be possible by way of an effective implementation mechanism designed and executed by the regulatory authorities through national legislations.

Principle 9 of the WHO GCP deals with informed consent. However the real issue in informed consent process is the level of understanding of the participant and his ability to understand the issues involved by way of participation, which may depend on the level in respect of which, both the investigator and the participants are able to communicate, the social and educational background of the participant and there should be meeting of mind in the real sense, ie consensus ad idem between the investigator and the trial participant. Principle 10, does not specifically mention the qualification of the investigator rather mentions the requirements of license only where it is required.

Principle 11 mentions about the need to record, and store the clinical trial related information and Principle 12 specifies the confidentiality requirements. However in both the cases the period of retention of data / period of confidentiality requirements not specified. The tenure of confidentiality will be as per the
applicable regulatory requirements, which may vary from country to country. The Contract Research Organisations may also look at countries where the regulatory requirements are less stringent, which may have a significant reduction in the cost of conducting a clinical trial.

WHO in 2000 has published an Operational Guidelines for Ethics Committees That Review Biomedical Research, with an object to complement existing laws, regulation and practice and to contribute to the development of quality and consistency in the ethical review of biomedical research? The purpose of an EC is in reviewing biomedical research is to contribute to safeguarding the dignity, rights, safety, and well-being of all actual or potential research participants.

Further, it states that the goals of research, while important, should never be permitted to override the health, well-being, and care of research participants. The primary responsibility is to protect the dignity of the individual, thereby giving paramount importance to the protection of human rights issue involved in the research. The Ethics Committee (EC) is required to be multidisciplinary, multi-sectorial to be established in accordance with the applicable laws and regulations of the country. The guidelines details on decision making, communicating a decision, conflict of interest, documentation and archiving, follow up etc.

Lack of training and expertise on ethical issues were considered as one of the draw backs of many ethical committees. However, the WHO guidelines mentions the conditions of appointment and state the provisions available for EC members to receive introductory training in the work of an EC as well as ongoing opportunities for enhancing their capacity for ethical review. The guideline


\footnote{Id, at p.6.}
recommends for archival of the documents for a minimum period of 3 years following the completion of a study\textsuperscript{103}.

With a view to strengthen the ethical review throughout the world, WHO has set up the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER), which is a network of independently established regional fora for ethical review committees, health researchers and invited partner organizations. The primary objective of SIDCER is to contribute to human subject protections globally by developing local capacity for ethical review of research involving human subjects and for developing policies on the ethics of health research\textsuperscript{104}.

WHO has set up an International Clinical Trial Registry Platform (ICTRP), with an objective to facilitate prospective registration of the Trial Registration Data Set on all clinical trials, and the public accessibility of that information, which also enhance access to information by patients, families, patient groups and others\textsuperscript{105}. Publication bias was one of the major issues which prevented dissemination of knowledge and information in clinical research. Communication of the research outcome was of paramount importance in assisting the medical fraternity in taking appropriate treatment decisions and also in the public interest.

WHO has also issues international standards for clinical trial registries, stating that the registration of all interventional trial as a scientific, ethical, moral responsibility. The standard prescribed depicts minimum and ideal standards and also ensure quality and validity of data by adopting a process in plan to make sure that the registered data is complete and accurate. The International Committee of Medical Journal Editors (ICMJE) has proposed comprehensive trials registration as a solution to the problem of selective awareness and announced that all eleven ICMJE member journals will adopt a trials-registration

\textsuperscript{103} Id, at.p.18


policy to promote this goal. The ICMJE member journals will require, as a condition of consideration for publication, registration in a public trials registry. Trials must register at or before the onset of patient enrolment.\textsuperscript{106} Further, data transparency and disclosure is required to restore the public confidence in clinical trials, which was eroded due to various scandals and alleged manipulations.\textsuperscript{107}\textsuperscript{107} As noted by ICMJE, altruism and trust lie at the heart of research on human subjects as altruistic individuals trust that their participation will contribute to improved health for others and that researchers will minimize risks to participants. In return for the altruism and trust that make clinical research possible, the research enterprise has an obligation to conduct research ethically and to report it honestly.

When research sponsors or investigators conceal the presence of selected trials, these studies cannot influence the thinking of patients, clinicians, other researchers, and experts who write practice guidelines or decide on insurance-coverage policy. If all trials are registered in a public repository at their inception, every trial’s existence is part of the public record and the many stakeholders in clinical research can explore the full range of clinical evidence.\textsuperscript{108}

The proposal by the WHO to submit all clinical trials to a public registration system is a crucial first step to promoting transparency and accountability of medical research that will benefit all interested parties. Registration is based on the presumption that basic transparency is of crucial benefit to the public generally, and to research subjects who volunteer to participate in clinical trials.


particularly. But WHO ICTRP is still a voluntary system, relying on the
consciences of researchers for compliance, as it says, 'The registration of all
interventional trials is a scientific, ethical and moral responsibility.'

5.1.11 TRIPS : As per the TRIPS Agreement, the members are having an
obligation to protect the undisclosed information, data submitted to government
and government agencies, to ensure effective protection against unfair
competition as provided in the Paris Convention (1967). It also mandates that
the Natural and legal persons shall have the possibility of preventing information
lawfully within their control from being disclosed to, acquired by, or used by
others without their consent in a manner contrary to honest commercial
practices so long as such information: – is secret in the sense that it is not, as
a body or in the precise configuration of its components, generally known among
or readily accessible to persons within the circles that normally deal with the kind
of information in question; – has commercial value because it is secret; and –
has been subject to reasonable steps under the circumstances, by the person
lawfully in control of the information, to keep it secret. The disclosure is
protected against unfair commercial use, unless it is against public interest. This
is fact relevant to clinical trial as it protects the commercially valuable information
against disclosure and unfair usage.

5.1.12 Clinical Trial Regulatory System – USA

On May 18, 1990, during a commencement speech at Morgan State University,
President Bill Clinton has set a goal to develop an AIDS vaccine within a decade,

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109 T. Lemmens, & R. Bouchard, Comments on the Legal, Regulatory and Ethical Aspects of the
WHO Clinical Trial Registry Platform, Submitted as part of the Formal Consultation on Disclosure
Timing Policy available at http://www.who.int/ictrp/011_Lemmens_Bouchard_5April06.pdf. (Last
visited on June 18, 2014).

110 WHO, INTERNATIONAL CLINICAL TRIAL REGISTRY PLATFORM, available at

111 Article 39.1, Protection Against undisclosed Information, Trade Related Aspects of Intellectual
setting a "new national goal for science in the age of biology". However the pursuit for development of an effective preventive HIV Vaccine still continues.

The public health policy of US encourages the testing and disclosure of HIV status, however many states have enacted laws to penalise the potential HIV transmission and exposure.

A bill was introduced in the US House of representatives ‘Real Existing Policies that Encourage and Allow Legal HIV Discrimination Act of 2013’ with the object of preventing discrimination of use of civil and criminal laws against people who tested positive for HIV. But the bill was not enacted.

The U.S. Food and Drug Administration (USFDA) is the regulatory authority in USA for conducting and evaluating clinical trials. According to medical historian Harry Marks, the modern controlled clinical trial is largely an American invention as statistically-based clinical trials became a critically important part of evidence-based medicine in the U.S. following World War-II.

The U.S. Food and Drug Administration is the oldest federal agency dedicated to consumer protection, originating as a single chemist appointed to the U.S. Department of Agriculture in 1862. The Federal Food and Drugs act, 1906 (Wiley Act) was one of the progressive legislation enacted in United States with the object of preventing the manufacture, sale or transportation of adulterated or

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mislabeled or poisonous or deleterious foods, drugs, medicines and for regulating the traffic therein and for other purposes. The predecessor of FDA was the Division of Chemistry and then (after July 1901) the Bureau of Chemistry.

The modern era of the FDA dates to 1906 with the passage of the Federal Food and Drugs Act 1906, though the name of Bureau of Chemistry’s was changed to the Food, Drug, and Insecticide Administration (FDIA) in July 1927, when the non-regulatory research functions of the bureau were transferred elsewhere in the department. In July 1930 the name was shortened to the present version. Between 1906 and 1938, legal proceedings over many problems with dangerous drugs demonstrated that the Pure Food and Drugs Act did not go far enough to protect public safety. The enactment of the Food, Drug, and Cosmetics Act (FD &C) in 1938, culminated due to a tragic event that killed scores of patients, including many children, by an untested pharmaceutical as soon as it went on the market.

US FDA is clothed with the responsibility of active monitoring of the conduct and evaluation of clinical trials. The Code of Federal Regulations (CFR) Title 21 are the regulations related to Food and Drugs. Part 50 of the Regulations deals with the protection of human subjects and Part 56 is on the Institutional Review Board (IRB), which describes the general standards for the composition, operation, and responsibility of an Institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and Drug Administration, as well as

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119 J. Peppercorn, supra note 2.
the clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration. In addition certain federally sponsored research is subject to the regulations of the Food and Drug Administration (FDA) at 21 CFR parts 50 and 56. The FDA regulations mandate financial disclosures by the Clinical Investigators. This could enable the stakeholder to identify any potential conflict of interest.

The Regulations defines minimal risk. As defined minimal risk means that the probability of harm or discomfort anticipated in the research are greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Six different parts of the regulations use the concept of minimal risk, including parts that apply to

- research on children;
- research on prisoners;
- research on fetuses;
- procedures for altering the elements of informed consent;
- procedures for waiving documentation requirements; and
- expedited review of research.

Although minimal risk plays a key role in the United States’ (US) federal research regulations, it has generated considerable controversy. Under 21 CFR 56.III (a), one of the criteria for IRB approval of research is that the IRB must determine that the risks to the subjects are minimized.

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A preventive HIV vaccine trial participant can face short term as well as long term risks for both adults and adolescents. There could be increase in level of antibody and the subjects are most likely to be left HIV positive (without an HIV infection) for an unknown duration using commercially available HIV tests and thus would be subject to potential discrimination and other consequences in the absence of documentation of their participation in a clinical investigation.

- Other risks associated with enrolment of adolescents included:
- The effects of vaccination on risk-taking behaviour are unknown.
- Risk reduction programs and counseling offered in the protocol are also of unknown effect in this age group.
- The future impact of vaccination with this or other HIV vaccines on future vaccination options, HIV infection, and HIV treatment options is not known.

It was unknown at the time that the vaccine could increase the risk of acquiring HIV infection\textsuperscript{125}. The risk exposure for an adult healthy participant is more compared to a non-participating individual and the participant will get any benefit from a preventive HIV vaccine trial, though the community may be benefitted is doubtful. So it can be argued that the standard of minimal risk will be difficult to apply for a preventive HIV vaccine trial.

The Code of Federal Regulations (CFR) defines ‘Clinical investigation\textsuperscript{126}’ as any experiment that involves a test article and one or more human subjects, subject to requirements for prior submission to the Food and Drug Administration under Section 505(i) or 520(g) of the Act, or the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.

The term does not include experiments that are subject to the provisions of Part 58 of this chapter, regarding nonclinical laboratory studies. The definition of *Test Article*\textsuperscript{127} means any drug (including a biological product for human use), which will cover vaccine as well. This definition is broad enough to cover any drug related experiments involving human subjects and are different from many of the prevailing definitions of clinical trial in different national legislations and in various internationally accepted guidelines.

The Belmont report was adopted by the U.S. Department of Health and Human Services as regulations governing all research involving human subjects supported or conducted by the Department. These set of rules, referred to as the Common Rule\textsuperscript{128} were later adopted by other federal agencies that conduct or support research. All U.S. government funded human subject’s research, domestic and international, is governed by the Common Rule.

The Common Rule sets forth requirements for review by an Institutional Review Board (IRB), informed consent process, and additional protections for vulnerable populations\textsuperscript{129}. The Common Rule governs 18 federal departments and agencies. The Common Rule applies to research conducted at or funded by the agencies that have adopted it, though it has not been adopted by all agencies that fund research. This means that, in order to be eligible to receive funding from one of the agencies that has adopted the Common Rule and/or other subsections of 45 CFR 46, researchers and institutions must abide by the relevant regulatory provisions. It also means that federal law does not require research conducted without federal money (or with money from an agency that has not adopted the Common Rule and/or other Subparts of 45 CFR 46) to be conducted in accordance with these regulations. A number of private companies

\textsuperscript{127}Id.


have voluntarily chosen to follow the Common Rule, though these are not subject
to federal enforcement mechanisms if they fail to comply.\textsuperscript{130}

The health privacy rule is one of several new standards mandated by the
administrative simplification provisions of the Health Insurance Portability and
Accountability Act of 1996. As per HIPA Act, the privacy regulation applies to
three groups of entities:

(i) individual and group health plans that provide or pay for medical care;

(ii) health care clearinghouses (i.e., entities that facilitate and process the
flow of information between health care providers and payers); and

(iii) health care providers who transmit health information electronically in a
standard format in connection with one of the HIPAA-specified
transactions, or who rely on third-party billing services to conduct such
transactions.

The rule, therefore, does not apply directly to other entities that collect and
maintain health information such as life insurers, researchers, employers (unless
they are acting as providers or plans), and public health officials.\textsuperscript{131}

Section 505 of the FD&C (21 U.S.C. Sec. 355) provides that no person may
introduce a new drug into interstate commerce without first filing an application
with the FDA. This section of the law specifies the general content of such an
application. The FDA promulgated regulations implementing this section of the
FD&C at 21 C.F.R. S 312. In 1991, the FDA and the Department of Health and
Human Services (DHHS) adopted the so-called “Common Rule” intended to
protect the rights of human subjects enrolled in clinical trials. This is codified at
45 C.F.R. Part 46 Subpart A for those clinical studies conducted by or with the

\textsuperscript{130} E.D. Williams, Federal Protection for Human Research Subjects: An Analysis of the Common
Rule and Its Interactions with FDA Regulations and the HIPAA Privacy Rule (2005), CRS report
for Congress, available at http://www.fas.org/sgp/crs/misc/RL32909.pdf; (Last visited on
December 12, 2014).

\textsuperscript{131} C. S. Redhead, Medical Records Privacy: Questions and Answers on the HIPAA Final Rule,
CSR Report for Congress (2003), available at https://epic.org/privacy/ medical/ RS 20500
.pdf,(Last visited on December 12, 2014).
support of federal agency or department and at 21 C.F.R. Parts 50 and 56 for those products subject to FDA regulation; the former are discussed in greater detail in a later section of this paper.

Though regulatory agencies across the globe have a duty to protect the public from unreasonable risk and to promote the development of medicines that improve health, the degree of involvement varies among countries. In US, FDA encourages meeting with vaccine developers, sponsors, at three points before the development process, before the first clinical trial and submission of clinical trial application, (Investigational New Drug), after the phase II clinical trial, and before the marketing (licensure) application. AIDS Vaccine may rise certain additional regulatory issues, one is that the HIV Vaccine may be developed in European Union or USA, but intended for the use in Asia, African or any other less developed countries. Although the vaccine must meet the fundamental requirements for safety, their risk benefit considerations may vary with the countries infection rate and other local factors.

5.1.12.1 Informed Consent

A legally effective informed consent, which should minimize the possibility of coercion, undue influence, without having any exculpatory language which may waive the legal rights and grants the sponsor, investigator etc for a release from liability of negligence is mandatory, for any investigator to involve a human being in clinical research. Though the regulations does not insist for an audio or video recording of the informed consent process, the guidance documents issued by FDA recommends a video tape recording of the consent interview, besides the requirement of an impartial third party witnessing the entire consent process and sign the consent document, in case of illiterate English speaking

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133 21 CFR 50.20, supra note 10.
subjects. The Regulations also provide exceptions to the general requirements of informed consent, however the same may have least application in preventive HIV vaccine clinical trial.

The elements of Informed consent as stated in the regulations include a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subjects participation, a description of the procedures to be followed and identification of any procedures which are experimental, description of any reasonable foreseeable risks or discomforts to the subject, for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

There are similarities in the informed consent process followed in clinical trials in other jurisdictions, international guidelines etc, the issues related to capability of the applicant to understand the risks involved is not expressly addressed. However the social realities and better law enforcement mechanisms in developed countries like US, may pose less risk to participants of underdeveloped countries. Any act done which is not falling within the process consented, may amount to assault and may expose the investigator liable for damages. The court of Appeal in Mary E. Schloendorff v. The Society of the New York Hospital, observed that

In the case at hand, the wrong complained of is not merely negligence. It is trespass. 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, for which he is liable in damages.

135 21 CFR 50.25, supra note 10,
136 211 N.Y. 125, 105 N.E. 92 (1914)
Though the relationship between a clinical trial participant and investigator is not that of a patient and doctor, and an investigator also has a legal obligation to inform the subject of the risk involved consequence of his participation in the trial. Preventive HIV Vaccine trials are conducted in healthy individuals and the subject knows nothing on the risks involved in an HIV vaccine trial and the investigator is better equipped to inform the subject on the risks involved and to enable him to take an informed decision. The trial participant has to rely on the expertise and competence of the investigator. The real issue could be, the risks involved in participation of an HIV vaccine trial may include known and unknown risks and whether a failure to inform on a risk which is not expected at the time of enrolment in the trial can also vitiate the participation in the trial.

A physician occupies a position of trust and confidence as regards his patient - a fiduciary position. It is his duty to act with the utmost good faith. This duty of the physician flows from the relationship with his patient and is fixed by law - not by the contract of employment. Full disclosure by the physician is necessary for an informed consent by the patient\(^{37}\). However physicians are generally obliged to advice and inform the patients on the medical risks involved and not on other risks\(^{38}\). Since investigator-subject relationship is not considered to be a doctor-patient relationship, even in case the investigator is a doctor, should the investigator of an HIV vaccine trial be obliged to inform the participant beyond medical risks, some of which may not be his core competency is debatable.

The regulations address the concept of research involving more than minimal risk in favour of the trial participants. The regulations do not address the quantum of compensation payable.

The principle of justice and fairness recognizes that the benefits and burdens of research should be distributed equitably. A system of compensation for research-related injury can help redistribute benefits to those disproportionately burdened.


\(^{38}\) Southard v. Temple University Hospital, 781, A.2d.101(2001).
as a result of participating in research, that is, those injured as a result of participation\textsuperscript{139}.

5.1.12.2 Confidentiality and Privacy issues

The Americans with Disabilities Act (ADA), makes discrimination on the basis of disability as unlawful. In a landmark case \textit{Bragdon v. Abbott}\textsuperscript{140}, the U.S Supreme Court ruled that HIV infection was found to meet the definition of disability under the ADA and even the advisory opinion of American Dental Association enumerates that a decision not to provide treatment to an individual because the individual has AIDS or is HIV seropositive, based solely on that fact, is unethical\textsuperscript{141}.

Though the Supreme Court judgment has upheld the rights of the patient, it was criticized that it has not sufficiently settled the interpretation of the ADA’s definition of disability to provide HIV Vaccine trial participant any measure of security against any prospective social harms. A false-positive HIV test may or may not lead to liability if used against a given plaintiff. Without a stronger sense of the scope of protection afforded by the ADA, HIV vaccine trial participants cannot rely solely on the Act to shield them from discrimination based on vaccine sero positivity. More significantly, disability law does not extend to discrimination based on AIDS vaccine trial participation\textsuperscript{142}. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) protects the privacy of patient’s medical records and rules and was effective in preventing discrimination against people living with HIV/AIDS by preventing others from knowing the HIV status.


\textsuperscript{140} 524 U.S. 624 (1998).

\textsuperscript{141} Id.

In response to a congressional mandate in the Health Insurance Portability and Accountability Act of 1996 (HIPAA), HHS issued regulations entitled *Standards for Privacy of Individually Identifiable Health Information.* For most covered entities, compliance with these regulations, known as the Privacy Rule, was required as of April 14, 2003.

The Privacy Rule is a response to public concern over potential abuses of the privacy of health information. The Privacy Rule establishes a category of health information, referred to as PHI, which may be used or disclosed to others only in certain circumstances or under certain conditions. PHI is a subset of what is termed *individually identifiable health information.* With certain exceptions, the Privacy Rule applies to individually identifiable health information created or maintained by a covered entity. Covered entities are health plans, health care clearinghouses, and health care providers that transmit health information electronically in connection with certain defined HIPAA transactions, such as claims or eligibility inquiries.

Researchers are not themselves covered entities, unless they are also health care providers and engage in any of the covered electronic transactions. If, however, researchers are employees or other workforce members of a covered entity (e.g., a hospital or health insurer), they may have to comply with that entity’s HIPAA privacy policies and procedures. Researchers who are not themselves covered entities, or who are not workforce members of covered entities, may be indirectly affected by the Privacy Rule if covered entities supply their data.

In addition, it should be noted that the HHS and FDA’s Protection of Human Subjects Regulations (45 CFR part 46 and 21 CFR parts 50 and 56, respectively) may also apply to clinical research. The Privacy Rule also permits, without Authorization, covered entities to make a number of other disclosures of PHI.

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including disclosures that are required by law, disclosures to public health authorities authorized by law to collect or receive such information for public health activities, and disclosures for adverse event reporting to certain persons subject to the jurisdiction of the FDA\textsuperscript{144}.

The Freedom of Information Act (FOIA) which was enacted in 1996 provided that the public may request access to information revealing the workings of federal agencies, unless the information falls within one of nine statutory exemptions. Exemption 4 of the Freedom of Information Act, protects ‘trade secrets and commercial or financial information obtained from a person that is privileged or confidential. This exemption is intended to protect the interest of both the government and submitters of the information\textsuperscript{145}. The clinical trial data falls within the ambit of commercial information and the public is barred from access to such data held by the FDA in view of the exemption granted under the Act.

Clinical trial data collected by pharmaceutical manufacturers is commercially valuable as it is costly to acquire and may provide the basis for FDA approval of a product. The clinical trial data fall within most of the states’ broad definitions of \textit{trade secrets}. Pharmaceutical manufacturers make two formal data submissions to the FDA in connection with new drugs: (1) an Investigational New Drug (IND) application before initiation of human trials, and (2) a New Drug Application (NDA) reporting clinical trial results before marketing\textsuperscript{146}.

The FDA can make specific data available upon public request in narrow circumstances: If the application is not approved, all other avenues of appeal are


\textsuperscript{146} A. S. Kesselheim and M. M. Mello, \textit{Confidentiality Laws And Secrecy In Medical Research: Improving Public Access To Data On Drug Safety}, HEALTH AFFAIRS, 26(2) \textit{available at} http://content.healthaffairs.org/content/26/2/483.full,( Last visited on December 10,2014).
exhausted, and no further work is being done on the application\textsuperscript{147}. Information gathered in support of applications that the FDA does not approve may still be of particular interest in the case of “supplemental NDAs,” where a manufacturer seeks approval for a new use of a drug that is already on the market. Clinical trials in the supplemental NDA can shed more light on an already-approved medication; however, notably, the FDA does not question or evaluate a sponsor’s claim that further work will be done on an unapproved drug.

These rules reflect the FDA understands that research data are entitled to protection as proprietary information. Part of the rationale is to prevent competitors from using data on safety and effectiveness gathered by another manufacturer to obtain approval of generic alternatives or similar drugs within the same class. The FDA originally adopted the broad Restatement approach, considering as a trade secret all nonpublic data submitted in the drug approval process\textsuperscript{148}.

However, the scenario has changed considerably with the setup of clinical trial registry and the enactment of Food and Drug Administration (FDA) Amendments Act of 2007 (FDAAA). The sharing of data and clinical studies shielding the participants’ privacy and commercially confidential information has become imperative and in the public interest. Shielding the clinical trials can be dangerous especially in preventive HIV vaccine clinical trials. Disclosing safety data from clinical trials would allow protection of most commercially valuable information and better balance our interests in drug innovation and patient safety\textsuperscript{149}.

The Patient Protection and Affordable Care Act added a new provision to the Federal Public Health Services Act, which mandates a health insurance company to cover routine costs associated with approved clinical trials. The Act also defines approved clinical trials means as a phase I, phase II, phase III, or phase

\textsuperscript{147} 21 CFR 314.430(f) 2005,
\textsuperscript{148} 21 CFR 314.14
\textsuperscript{149} WMA General Assembly, Supra Note 33.
IV clinical trial that is conducted in relation to the prevention, detection, or treatment of 13 cancer or other life-threatening disease or condition. The Insurance Company shall not discriminate the individual against the individual based on individual’s participation in the clinical trials.\textsuperscript{150}

Partner notification laws prevailing certain states including New York\textsuperscript{151} was always a subject matter of controversy. The seropositivity of a HIV Vaccine trial participant can also be misconstrued and notified to the partners. Even if it can be established to be seropositivity by a HIV vaccine trial participant, the fear and chances of any medical complications, however remote it could be, may impact the social life of the HIV vaccine trial participant, as partners tend to stay away from such people.

5.1.12.3 Clinical Trial Registry

The FDA Modernization Act 1997 requires the Secretary of Health and Human Services (HHS) to establish a data bank of information on clinical trial for drugs for serious or life threatening diseases and conditions. It also requires dissemination of the information through information systems, which shall include toll free telephone communications, to the public and health care providers and to researchers.\textsuperscript{152}

Title VIII of the Food and Drug Administration (FDA) Amendments Act of 2007 (FDAAA) amending section 402 of the Public Health Services Act, mandates for registration and submission of summary results information other than phase I trials with National Institute of Health(NIH), ClinicalTrials.gov, for applicable clinical investigation, clinical trial of drugs and devices as defined in the Act. The responsible party for registration and publishing the results of the trial is the

sponsor of the clinical trial or the principal investigator of the clinical trial, if so designated by sponsor, contractor, etc, so long the principal investigator is responsible for the conduct of the trial. In case of clinical trial of life threatening diseases, the clinical trial information in compliance with the Act needs to be submitted within 21 days from the date of enrolment of the first patient. The law also mandates that the clinical trial information submitted by the responsible party shall not be false or misleading. The FDAAA also imposes civil money penalties for noncompliance of the provisions of the Act and directs that the federal agencies shall verify the submission of clinical trial information by the grantee to ensure compliance before releasing remaining or allocating future grant funding\(^{153}\). The FDA also insists for a certificate in compliance with the clinical trial requirements in Form FDA 367 along with any Investigational New Drug Application (IND), New Drug Application (NDA) etc.

The Clinical trial registry submission is required to include a statement to the effect that a description of this clinical trial will be available on designated trial registry website as required by U.S. Law and the website will not include information that can identify the participant, however the website will include a summary of the results which can be searched at any time\(^{154}\).

Historically US protected confidential information; however the law needs to strike a balance between the interest of the Companies who are developing valuable commercial information through clinical research as well as public interest with regard to dissemination of the information. Dissemination of trial data is critical in HIV vaccine trials to avoid any repeated failures. US regulations has also safeguarded against submission of any incorrect or misleading


information in compliance with the clinical trial registration requirements. The informed consent requirements related to clinical trial registry is intended to protect the privacy of the participants, which is more crucial in a preventive HIV vaccine clinical trial considering the potential social harms that may be faced by a participant.

5.1.12.4 Institutional Review Boards / Ethics Committee

Under FDA regulations, an IRB means any group, board, or committee, or other group formally designated by an institution to review, approve the initiation of, conduct the periodic review of biomedical research involving human subjects. IRB has the authority to approve, require modifications in (to secure approval), or disapprove research and has an important role in the protection of the rights and welfare of human research subjects.

It is an independent decision making authority with the responsibility and power to protect the trial participants. An IRB should consist of not less than five members who are experts in the relevant areas from varying back grounds and is expected to review the procedures and the research protocol to ensure adequate protection to the subjects. There are few exemptions from IRB requirements as mentioned in the Code of Federal Regulations. Barring those exemptions, any clinical investigations which should meet the prior submission to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by IRB meeting the requirement of the regulations. On applications by a sponsor or sponsor –investigator, FDA may waive any of the requirements under the regulations including IRB requirements or any research activity or classes of research activity. Many studies that focus on non-FDA regulated therapies are subject to HHS regulation, but only if they are “conducted, supported or otherwise subject to regulation by any federal department or agency.

IRBs are required to be mandatorily registered under the Regulations, before it can be designated as an assurance approved for federal wide use by Office of
Human Rights Protection under Sect 46.103(a). There is no bar on the remuneration payable to the members of IRB, nor there is any reduction in IRBs liability in malpractice suits by virtue of the Federal Regulations. Any change in research activity, including conclusion of the trial is required to be reported to IRB. The FDA regulations do not preclude a member from being compensated for services rendered. However payment to IRB members should not be related to or dependent upon a favorable decision\textsuperscript{155}. 

The guidelines issued to IRBs by OHRP cautions that the IRB should be aware of other risks associated with vaccine trials, including the possibility that vaccines produced synthetically or using recombinant DNA techniques may present risks as yet unknown, that groups often most likely to benefit from receiving a vaccine are often the most vulnerable to coercion (e.g., institutionalized persons or children), and that subjects in control groups may erroneously assume that they have been immunized.

FDA regulations require that subjects be provided with written instructions about whom to contact in the event of serious adverse reactions or research-related injury\textsuperscript{156}. IRB records related to the review of a clinical trial must be retained for at least three (3) years after the completion of the research. The records are also required to be accessible for inspection and copying by FDA at reasonable time, in a reasonable manner\textsuperscript{157}. The Regulations\textsuperscript{158} also stipulate the criteria for satisfaction of IRB approval of research, which includes risks to subjects are minimized, risks to subjects are reasonable in respect of the anticipated benefits, selection of subjects are equitable etc. However if we consider the approval

\textsuperscript{155} CODE OF FEDERAL REGULATIONS
\textsuperscript{156} OHRP: INSTITUTIONAL REVIEW BOARD GUIDELINES, Chapter 5, Section C, Vaccine Trials, \textit{available at} https://www.research.uky.edu/ori/ORIForms/T4-Vaccine-Trials.pdf, (Last visited on December 19, 2014).
criteria for a preventive HIV Vaccine trial, it would be difficult to justify in view of the social harm a participant may face, besides other potential complexities. The participant will not be personally benefited, though any positive result will be in the best interest of the community.

IRB members are also not free from legal risks. The risks may arise from breach of duty, conflict of interests, negligence, bias etc. IRB reviews are not subject to public and media scrutiny, which will safeguard the confidentiality of the subjects and also save the members of IRB from adverse publicity and unwarranted criticism.

Another area of risk concerns the proper management of conflict of interest both within the IRB and on the part of the investigator. Although the regulations ban IRB members from participating in the review of a protocol in which there is a conflict of interest, what would constitute a conflict of interest for these purposes is not defined. Traditionally, the obvious conflict that has been managed well by most IRBs is the IRB member who would directly participate in the research as a principle investigator (PI) or sub-investigator. In these situations, most IRBs have been able to identify the PI as having a conflict and have moved to exclude that person from the discussion and voting on the protocol.

Other forms of institutional conflicts have also been relatively well managed by IRBs. These include those members of the IRB who may have an interest in the protocol by being a member of the same academic department. Of course, this type of conflict can be either a conflict in favor of a protocol, or against it, given the realities of the politics within academic institutions. Again, it can be relatively simple to identify this type of conflict and to exclude the conflicted member from the discussion and vote on the protocol. It is essential that these types of conflicts be noted in the minutes and the action taken to protect against the conflict documented\(^{159}\).

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\(^{159}\) D.L. Icenogle, *et al.*, *IRBs, Conflict and Liability: Will We See IRBs in Court? Or is it when?*, *Clinical Medicine and Research*, 1 (1), available at
Earlier in response to an amendment proposed to the informed consent regulations by the FDA, one of the comments received suggested that an independent ombudsman who is aware of the acute risks of the specific research, the long term risks of the research for the individual, family, society based on the condition of the potential subject be appointed to oversee the study. This was not agreed by the agency on the ground that the current regulations require the consent form to contain an “explanation of whom to contact for answers to pertinent questions about the research and research subjects’ rights, and whom to contact in the event of a research-related injury to the subject.” It may be the IRB or some other designated individual who performs these ombudsman-type functions for these investigations\textsuperscript{160}.

The FDA regulations does not specify any appeal provision against the decision of the IRB, though some of the Institutional Review Board operating procedures specify for a appeal provision against a named authority within the institution conducting the research, nor there is any specific safe guarding provisions to avoid bias of the members of the IRB. HIV preventive vaccine trials are unique due to its complexity and risks associated with the participants, however there is no specific guidance for minimizing the potential risks, social harms which a HIV preventive trial participant may be exposed.

5.1.12.5 Trial related Injury and Compensation

In US, the research institutions are not mandated to provide free medical care or compensation to clinical trial participant for the trial related injuries. Under the Code of Federal Regulations the research institutions are mandated to explain whether any medical treatments are available or not.

The elements of informed consent as stated in the FDA regulations also mentions that for research involving more than minimal risk, an explanation as to whether any compensation and medical treatments are available if injury occurs, the details and where further information could be obtained. An explanation as to whom to contact in case of research related injuries and also to get answers on subjects rights to be provided\textsuperscript{161}. Institutional Review Board has the ethical responsibility to raise the bar when necessary to ensure that the adequate provision for free or compensated medical care for research related injury and they have the regulatory authority to enact these provisions as they deem fit. The Regulations also exempt certain clinical investigation from the compliance requirements, under the part of the Regulations\textsuperscript{162}.

The Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) has published modules on compensation for research-related injury.

The "Compensation Background" module describes the goals of compensating individuals for research-related injury; provides ethical justification for compensation; discusses practical considerations, including informed consent and cost and feasibility. The module presents various models of compensation including insurance, personal insurance, specialty courts, and compensation funds\textsuperscript{163}.

The National Vaccine Injury Compensation Program (NVICP) was created under the National childhood Vaccine Injury Act 1986(PL-99-660) enacted by congress to institute vaccine safety reforms in U.S. mass vaccination system and to create federal no fault, non – adversarial alternative to suing vaccine

\textsuperscript{161} 21 CFR 50.25.
manufactures and providers in civil court. Section 22 (b) (1) pre-empts certain claims against the manufacturer if the injury or death associated with the administration of a vaccine if the injury or death resulted from side effects that were unavoidable even though the vaccine was properly prepared and was accompanied by proper directions and warnings. NVICP covers medical costs, attorney fees, lost wages, and claims for pain and suffering. Awards typically consist of an initial lump sum plus a lifetime annuity. However this legislation will not provide compensation for HIV vaccine related injuries.

The principle of beneficence as mentioned in the Belmont Report is the ethical basis for providing compensation. As per the principle of beneficence the persons needs to be protected from harm and their well being is required to be secured.

The quest for a HIV vaccine was never been free from controversies and frauds. Reports appeared in the media on a scientist charged with HIV vaccine fraud. US federal prosecutors have filed charges against a former Iowa State University laboratory manager, Dong-Pyou Han, after he falsified data that subsequently lead to millions of dollars in grants for an experimental HIV vaccine. Han who resigned from Iowa State University, admitted to spiking rabbit’s blood with human antibodies in an effort exaggerate the promise of the vaccine, and the irregularity was noticed by a laboratory in Harvard.

Despite being one of the most progressive countries in the world, US was not offering the best compensation for vaccine related injuries. The anti discrimination laws have addressed the issues against discrimination, issues related to insurance in a better manner. However it still not provided any solution

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to the entire social risks involved. The state penal laws for disclosure of HIV status, partner notification laws will add to the difficulties that may be faced by a HIV vaccine trial participant, though there could be a logical reasoning behind the legislative intent behind these laws.

5.1.13 Clinical Trial Regulatory System in European Union

The European Union Treaty explicitly states that health care is the responsibility of the member states\textsuperscript{167}. It was criticised that Health policy in the European Union (EU) has a fundamental contradiction at its core, as many national health activities are subject to EU law and policy, and the member state health system involves interactions with people, goods, and services, all of which have granted freedom of movement across the borders\textsuperscript{168}.

European Union has considered research on HIV/AIDS as a top priority. The European Commission communication on combating HIV/AIDS in the EU\textsuperscript{169} and neighboring countries identifies policies to help reduce the number of new infections and improve the quality of life for people living with HIV/AIDS. The Commission reiterates the need to amplify efforts in vaccine, including new technologies for vaccines, microbicides and in new therapeutics, research and development and also further encourages long-term public and private investment into research for the development of new and improved prevention technologies and treatments for HIV and associated infections.\textsuperscript{170} The Commission has also set up two bodies, HIV/AIDS Think Tank and HIV/AIDS


\textsuperscript{168} E. Mossialos, \textit{et al.}, Health Systems Governance In Europe: The Role Of European Union Law And Policy, P.4, (1\textsuperscript{st} edn, 2010) available at\textsuperscript{\url{http://www.euro.who.int/__data/assets/pdf_file/0007/138148/E94886_ch01.pdf?ua=1}}, (Last visited on November 10, 2014).


\textsuperscript{170} \textit{Id.}
Civil Society Forum, to help with policy implementation and strengthen cooperation among countries civil society and international organization\textsuperscript{171}.

Under the Seventh Framework Programme (FP7) the European Commission is pursuing the priorities identified in previous programmes to improve the prevention of future infections and the treatment of people living with HIV/AIDS. The aim is also to cover priority aspects of the infection/disease and to fill existing gaps, which were not previously addressed. During the first 3 years of FP7, a budget of approximately EUR 70 million has been committed to promote collaborative translational research on HIV/AIDS\textsuperscript{172}.

In the European legislative framework, the approval of clinical trial applications is the responsibility of the member states. The national competent authorities and the ethics committees are responsible for authorizing conducting of a clinical trial in the member state\textsuperscript{173}. The national competent authorities are responsible for entering protocol related information that has been submitted to their member state into the Eura CT database. The authorities also add to this information the authorization of the clinical trial and the opinion from the relevant ethics committee. Once entered, a sub-set of this information is displayed through the EU clinical trials register website\textsuperscript{174}.

The law related to clinical trials in European Union was significantly shaped by the Clinical Trial Directive and Good Clinical Trial Practice. The Directive 2001/20/EC\textsuperscript{175} of the European parliament on approximation of the laws, regulations and administrative provision of the member states relating to


\textsuperscript{173} Art.9, Supra Note 6.

\textsuperscript{174} EU Clinical Trial Register, available at http://www.clinicaltrialsregister.eu/nationalauthorities.html (Last visited on December 12, 2014).

implementation of good clinical practice in the conduct of clinical trials, 
Commission directive laying down principles and guidelines of good 
manufacturing practice in respect of medicinal products for human use and 
investigational medicinal products for human use, deals with the law related to 
clinical trials\textsuperscript{176}.

A guidance document on the request to the competent authorities for 
authorization of a clinical trial on a medicinal product for human use, notification 
of substantial amendments and the declaration of the end of the trial will also be 
issued\textsuperscript{177}. In order to obtain marketing authorization for human medicines in 
European Economic Area (EEA), compliance of clinical trial directive is 
mandatory for trials conducted in EEA. The clinical trials conducted outside EEA 
will have to comply with the ethical guidelines of Directive 2001/20/EC, adhering 
to Good Clinical practice (ICH Guideline –E6-R1) and Declaration of Helsinki\textsuperscript{178}.

The new EU Clinical Trial Regulation was adopted\textsuperscript{179} on the 16th April 2014, 
which will be replacing the European Clinical Trial Directive 2001/20/EC 
(EUCTD), which standardized the clinical trials in European Community. The new 
regulation shall come into force no sooner than 28\textsuperscript{th} May 2016, and at least six 
months after the publication of the notice , post verification of EU portal EU data 
base , that it has achieved full functionality and system meet the functional 
specifications\textsuperscript{180}. During the transition period, the sponsors are allowed to start 
clinical trials under the Directive 2001/20/EC (EUCTD)\textsuperscript{181}.

\textsuperscript{176} Id, COMMISSION DIRECTIVE 2003/94/EC of 8 October 2003, available 
at http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm, (Last visited on January 3, 
2015).

\textsuperscript{177} Endralex- Vol 10, clinical Trial guidelines available at http://ec.europa.eu/health/ 

visited in December 10, 2014).

\textsuperscript{177} Regulation (EU) No.536/2014, European Parliament and the Council, Official Journal of 

\textsuperscript{180} Art.82, Art.99, Id.

\textsuperscript{181} M.C. Bassiouni, supra note 9.
In the EU Clinical Trial Regulations 536/2014 among the potential problems in the final agreement, is the stipulation that master files from trials be kept for 25 years, out of step with internationally accepted practice of 15 years. There are also some decisions that are left up to member states, creating the potential for future problems if countries adopt incompatible rules\textsuperscript{182}. The claims of the subjects against sponsors, investigators, civil, criminal liability, issues of causality, level damages and sanctions should remain governed by national laws\textsuperscript{183}. As such the entitlements of subjects against the same claim, could differ across the European Union.

The new Clinical Trials Regulation says that information from Clinical Study Reports of trials should not generally be considered commercially confidential, once a marketing authorisation has been granted, the procedure or granting marketing authorisation has been completed, the application for marketing authorisation has been withdrawn\textsuperscript{184}. However at the same time the New Regulation also insists that the confidentiality of records and personal information of subjects remain protected in accordance with the applicable law on personal data protection\textsuperscript{185}.

\textbf{5.1.13.1 European Medicines Agency}

The European Medicine Agency (EMEA)\textsuperscript{186} began its operations replacing the Community’s earlier approval mechanisms, with the main responsibility of the protection and promotion of public health and animal health, through evaluation of medicines for human and veterinary use. The European Medicines Agency relies on the results of clinical trials carried out by pharmaceutical companies to

\textsuperscript{182} LONDON DECLARATION, supra note 7.
\textsuperscript{183} M.C. Bassiouni supra note 9.
\textsuperscript{184} M.C. Bassiouni supra note 9.
\textsuperscript{185} Art.55, London Declaration.
reach its opinions on the authorisation of medicines. It does not have a role in approval applications of clinical trials in European Economic Area (EEA). Although the authorisation of clinical trials occurs at Member State level, the EMEA plays a key role in ensuring that the standards of good clinical practice (GCP) are applied across the European Economic Area (EEA) in cooperation with the Member States. The Agency is responsible for the development, maintenance and coordination of the Eura CT database, which is used by national competent authorities to enter clinical-trial data from clinical trial sponsors and paediatric-investigation-plan (PIP) addressees. A subset of this data is made available through the European Union Clinical Trials Register, which the Agency manages on behalf of EU Member States\(^ {187}\).

**5.1.13.2 European Union Clinical Trials Directive 2001/20/EC**

The European Union Clinical Trials Directive 2001/20/EC aims at harmonising the conduct of Clinical Trials across European Union from a regulatory perspective and to provide a framework which sets out how clinical trials investigating the safety or efficacy of a medicinal product in humans must be conducted. Member States have transposed the requirements of the directive into national laws, regulations and administrative provisions. The approval of clinical trial applications is the responsibility of the member states\(^ {188}\). Within the European Union each member state has a regulatory agency that may meet with developers.

The Clinical Trials Directive aims at an exhaustive harmonization of the regulatory framework for clinical trials. However, it has achieved this aim only to a limited extent. This is due to the inconsistent application of the Clinical Trials Directive, due to various reasons including (1) Substantial amendments (2)
reporting of suspected unexpected serious adverse reactions (3) application of clinical trial directive only to interventional trials\textsuperscript{189}.

Prior to the entry into force of the Clinical Trials Directive, the rules for performing clinical trials varied significantly in the Community as they were based on differing regulatory approaches in the Member States. Since 2004, clinical trials performed in the EU are regulated by the Clinical Trials Directive. The primary purpose of this Directive is to ensure:

- The protection of the health and safety of clinical trial participants;
- The ethical soundness of the clinical trial;
- The reliability and robustness of data generated in clinical trials; and
- Simplification and harmonization of the administrative provisions governing clinical trial in order to allow for cost-efficient clinical research.

Subsequently to its entry into force, the Clinical Trials Directive has been complemented with a Commission Directive setting out the principles of Good Clinical Practice ("GCP"). The Guideline on "Good Clinical Practice – ICH E6" which has been agreed in the framework of the International Conference for Harmonization ("ICH") is \textit{de facto} recognised worldwide as the applicable standard for GCP\textsuperscript{190}. The Good Clinical Practice Directive 2005/28/EC is aimed at adoption of the principles and same standard of Good Clinical Practice by experts, individuals and other involved in the conduct of clinical trials and to strengthen the legal basis for requiring Member States to comply with the principles and guidelines of good clinical practice\textsuperscript{191}.


The obligation to report any suspected serious, unexpected adverse reactions to the competent authorities of the member states, and to the Ethics Committee are on the sponsor. The time limit given for reporting varies depending on whether it is fatal or life-threatening or otherwise. The reporting of all serious adverse events shall be the responsibility of the investigator. Except certain events the protocol or investigator brochure identifies are not requiring immediate reporting, all other serious adverse events shall be immediately reported. The adverse events and other laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported within the time periods as specified in the protocol. The sponsor shall keep detailed records of all adverse events which are reported to him and the investigator shall supply to the sponsor and Ethics committee with any additional information requested. The Directive states that it is without prejudice to the civil or criminal liability of the sponsor and the investigator. However it does not discuss about the liability of Ethics Committee or its members, jointly or individually, against negligence or breach of duty or breach of the Directives, as such is left open to the national legislations.

The Clinical Trials Directive was often criticized as having excessive red tape. The European Commission estimates that all the changes could save researchers €800 million a year. The implementation of the EUCTD did not result in the intended harmonization of clinical trial requirements across the six analyzed EU member states but in the leveling of clinical trial activities. The expected increase of clinical research activity aimed by the EUCTD has not occurred in Europe. In contrast, the number of trials decreased in central and north-west Europe.

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192 Art.17, supra note 9.
193 Art.16, supra note 9.
Regardless of where they are conducted, all clinical trials included in applications for marketing authorisation for human medicines in the European Economic Area (EEA) must have been carried out in accordance with the requirements of the Directive\textsuperscript{196} which implies that the clinical trials conducted in the EEA have to comply with European Union (EU) clinical-trial legislation and the Clinical trials conducted outside the EEA have to comply with ethical principles equivalent to those set out in the EEA, including adhering to international good clinical practice and declaration of Helsinki\textsuperscript{197}.

5.1.13.3 EU Clinical Trial Register

The EU Clinical Trials Register was launched by the European Medicines Agency (EMA) to provide the Public access to the information held in Eudra CT database\textsuperscript{198}. The information from the sponsor is loaded into the Eudra CT database by the national medicines regulatory authority. The authority adds to this information the authorisation of the clinical trial and the opinion from the relevant ethics committee. Information on third-country trials if these trials are part of a paediatric investigation plan, etc.

The European Medicines Agency (EMA) has decided to publish the clinical reports “that underpin the decision-making on medicines.” It was reported that EMA will publish data submitted as part of marketing applications starting January 1, 2015. Beginning July 1, 2015, the agency will provide access to reports relating to applications for line extensions of indications for existing medicines. Any information that is considered as commercially confidential will be redacted from the documents. The policy does not apply retroactively, so EMA

\textsuperscript{196} Id.
\textsuperscript{197} Id.
\textsuperscript{198} A data base of Clinical trials commenced in the community from 1\textsuperscript{st} May 2004 available at https://eudract.ema.europa.eu/results-web/index.xhtml#, (Last visited on December 16, 2014)
will only publish new data. The main concerns during the public consultation were (a) The concept of commercially confidential information and protection from unfair commercial use, (b) protecting patient confidentiality, (c) concept of raw data.

5.1.13.4 Data Protection and Health Information Privacy

The definition of ‘personal data’ as defined in the directive is very wide, which includes every aspect of a data subject and reflects the ambit of the protection guaranteed under the directive. The stringent definition, though with certain exceptions, poses serious challenge for utilising such data in any clinical trial research. The controllers as defined under the directive are required to observe certain principles while processing the personal data of data subjects.

The prohibition of processing special categories of data, e.g., the personal data concerning the ethnic origin, health or sex life is not applicable where there is an explicit consent from the data subject, subject to any prohibition imposed by the laws of the member states. However this restriction shall not be applicable to processing of data for the purpose of preventive medicine, medical diagnosis, the provision of care or treatment or the management of health care subject under national law or rules established by national competent bodies, subject to the obligation of professional secrecy or by another person also subject to an

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Art. 2(a) ‘personal data’ shall mean any information relating to an identified or identifiable natural person (‘data subject’); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity.

202 Art. 8, Id
equivalent obligation of secrecy. The exception does not explicitly cover clinical research or even development of preventive medicine.

The development of national electronic patient record systems has been taking place across Europe and is the subject of continuing discussions at the EU level\textsuperscript{203}.

Directive 95/46/EC\textsuperscript{204} of the European Parliament and of the Council applies to the processing of personal data carried out in the Member States under the supervision of competent authorities, in the member states and Regulation (EC) No 45/2001 of the European Parliament and of the Council applies to the processing of personal data carried out by the European Commission and the European Medicines Agency within the framework of this Regulation, under the supervision of the European Data Protection Supervisor. The withdrawal of informed consent should not affect the results of activities already carried out, such as the storage and use of data obtained on the basis of informed consent before withdrawal.

Articles 1 of Directive 95/46/EC and of Directive 2002/58/EC clearly state the ultimate purpose of the rules contained therein: to protect the fundamental rights and freedoms of natural persons and in particular their right to privacy, with regard to the processing of personal data\textsuperscript{205}.

When the information that is processed does not fall within the concept of "personal data", the consequence is that the Directive does not apply, pursuant


to Article 3 thereof. Identified or identifiable” focuses on the conditions under which an individual should be considered as “identifiable”, and especially on “the means likely reasonably to be used” by the controller or by any other person to identify that person. Information relating to dead individuals is therefore in principle not to be considered as personal data subject to the rules of the Directive, as the dead are no longer natural persons in civil law. However, the data of the deceased may still indirectly receive\textsuperscript{206}.

In HIV vaccine clinical trial, and in respect of HIV positive individuals, the data can be related to their partners and family members, which may even after their death, could affect their status and life, especially individuals who were having seropositivity, may show HIV positive during normal HIV lab testing, unless otherwise clarified through further testing.

The European Court of Human Rights in, Z Vs Finland\textsuperscript{207} had an occasion to consider whether the disclosure of HIV status of a person, as accessible to public in a criminal case amounts to violation of her right to privacy. In this case Z, a Finnish national was awarded compensation for non pecuniary damages, for violation of her right to privacy under the Convention. It was violated when her identity and medical condition and her HIV status was disclosed by the media during her husband’s criminal trial, who was also HIV positive. The material in question was accessible to the public as from the year 2002 and the identity and medical condition was disclosed in the Court of Appeal’s Judgment. It was held unanimously that the disclosure of the applicant’s identity and medical condition by the Helsinki Court of Appeal constituted a breach of Article 8 of the European Convention on Human Rights.

\textsuperscript{206} Id

The partner notification laws are considered to have public health benefits, at the same time, it infringes the privacy of the person unless the partner is not bound to keep it as confidential or the notification is voluntary.

The literature pertaining to partner notification and HIV provides compelling evidence that notifying partners of patients newly diagnosed with HIV/AIDS is an important ethical duty. Partner notification provides vital information to identified contacts and enhances the ability of public health professionals to contain the spread of HIV in the general population\textsuperscript{208}.

The legal context for partner notification varies within Europe. Some countries have wide-ranging legal obligations to enforce partner notification, others have laws that are not enforced, and some have no such laws. These laws most often apply to HIV, syphilis, gonorrhoea, chlamydia, hepatitis B and C. There is no clear correlation between the existence of laws that make partner notification compulsory and routine partner notification. Voluntary partner notification is still the rule in most countries in Europe\textsuperscript{209}.

5.1.13.5 Ethics Committee in European Union Member States

Approval from Institutional Ethics Committee (IEC) is required before starting an interventional clinical trial in Europe after the release of the Clinical Trial Directive. Research ethics committees in Europe are typically composed of scientists and lay members; of physicians, members from the nursing profession, members with legal expertise, a pharmacist, somebody with ethical expertise, a statistician, at least one representative of a patient organisation, and others. Their main


obligation is to review research protocols for clinical trials within a certain time frame\textsuperscript{210}.

A clinical trial may be initiated only if the Ethics Committee and/or the competent authority come to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored.\textsuperscript{211} However, the EU Directive is still not entirely enforced by all national countries such as the requirement that explicitly requests a single IEC approval within each national country. A guideline and recommendations\textsuperscript{212} were issued to establish a greater degree of scientific efficacy and procedural responsibility in the practices of Ethics Committees (ECs) in Europe on the basis of which ECs can develop their own specific written procedures, standard operating procedures for their functions within biomedical research.

The new Regulations\textsuperscript{213} mandates that the ethical review should be performed by an ethics committee in accordance with the law of the member states concerned, which gives a direction for the ethics committee to encompass aspects, addressed in part I of the assessment report as envisaged in the Directive, for authorization of the clinical trial. The risk and inconvenience for the subjects considering the characteristics of intervention compared to normal clinical practice and the safety measures including provision for risk minimization measures, monitoring, safety reporting and safety plan.

If the ethics committee issues a negative opinion, the member state can refuse to authorize a clinical trial. The directive also prescribes that the member states


\textsuperscript{211}Art.3.2., \textit{supra} note 9.


\textsuperscript{213}B.M. Meier, \textit{supra} note 23.
shall provide an appeal procedure in respect of such refusal. There is no uniformity in the provision for an appeal mechanism across Europe. The countries are having procedures as per the national laws. Some of the countries viz Austria, U.K, Bulgeria, Denmark etc provide for an appeal mechanism, whereas some countries viz Italy, Czech Republic, Ireland do not provide for an appeal mechanism\textsuperscript{214}.

An appeal provision against the decision of ethics committee is essential for a proper dispensation of justice in any jurisdiction, failing which wrong decisions could adversely impact the research industry as well as the subjects.

RECs should be accountable to their appointing body or authority, according to the provisions given in national law or in other documents issued by national competent bodies or institutions. The appointing authority should satisfy itself that the REC functions according to the applicable rules. RECs should provide sufficient information about their work – ethics review, research follow up, and other activities – to their appointing institution or authority by means of well structured regular reports, which should not reveal confidential details of the research or its participants. Such reports, in their entirety or in the form of an executive summary, should also be made available publicly, for example on a REC, institution, or regional authority web site\textsuperscript{215}.

Since the main function of ethics committee is to protect the subject and to ensure that the trial is conducted in a manner in compliance with the applicable regulations, the public accountability of the ethics committee is very significant. However at present there is no mandatory provision to make the decisions of the ethics committee public or to make it accessible to public masking the relevant


information which may affect the privacy of the individual. The appointment and
remuneration of ethics committee is by the sponsor or the appointing body, the
chances of bias in favour of the appointing authority cannot be ruled out. Though
the Guidelines and Recommendation for European ethics committee \(^{216}\)
mentions the procedure for constituting ethics committee, the manner of
appointment is left open to the discretion of the appointing authority, which may
affect the impartiality of the ethics committee.

5.1.13.6 Clinical Trial Insurance

In Europe a common legal framework for the insurance of subjects participating
to clinical research is set up by the EU Directive 2001/20/EC\(^{217}\). The Directive
mandates that a clinical trial may be undertaken only if provision has been made
for insurance or indemnity cover the liability of the investigator and sponsor\(^{218}\).
The Research Ethics Committees (RECs), have to consider in preparing their
opinion: (1) Provision for indemnity or compensation in the event of injury or
death attributable to a clinical trial; (2) Any insurance or indemnity to cover the
liability of the investigator and sponsor.\(^{219}\). The insurance requirement is still
mandatory in the New Regulation as well; however it is relaxed in respect of low
intervention clinical trials, if the possible damage could be covered by the
applicable compensation system already in place in the respective member
states\(^{220}\).

The Directive leaves the adequacy or inadequacy of the insurance and the
indemnification to the discretion of the Ethics Committee. In a preventive HIV
vaccine trial, the adequacy of insurance to protect the participant from any
possible long term complications will play a key role in the patient protection. It
also depends on the additional risks which could be foreseen by the Ethics
Committee, to ensure the safety and protection of the trial participants.

\(^{216}\) Humphrey, supra note 27.
\(^{217}\) M. C. Bassiouni, supra note 9.
\(^{218}\) Art.3(2)(f), M. C. Bassiouni, supra note 9.
\(^{219}\) Art.6 (h), (i), M. C. Bassiouni, supra note 9.
\(^{220}\) Art.76, B.M. Meier, supra note 23.
A claim may arise out of a defect in the research protocol, negligence of the investigators, or may arise out of a defect in the product. If the claim is with respect to defective product, which may lead to product liability issues to the manufacturer. However, with respect to product liability, pursuant to Directive 85/374/EC on product liability, it may be questionable whether the manufacturer could be held liable for its (putatively) defective product since the product may – when used within the scope of a clinical trial - either not have been put into circulation (yet), or the product may not have been manufactured with the aim of sale or was distributed by him in the course of his business.

A product is defective when it does not provide the safety which a person is entitled to expect, taking all circumstances into account including the time when the product was in circulation. The produces shall not be liable as a result of the Directive if he proves that he did not put the product into circulation, or the state of scientific and technical knowledge at the time when he put the product into circulation was not such as to enable the existence of the defect to be discovered.

Trial of a product in a controlled environment may not amount to circulation of the product and the knowledge which he possess at the time of trial was not sufficient to understand the defect if any of the product. The trial participant is well aware that the drug is to be tested, which could have a chance of failure as well. This emphasizes the need for a comprehensive clinical trial insurance coverage to protect the trial participants.


5.1.13.7 Informed Consent

The Directive 2001/20/EC \(^{223}\) relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use defines informed consent. The Directive requires that the informed consent must be in writing, dated and signed by the subject, after being informed of the nature significance, implications and risks. If the person concerned is unable to write then, oral consent in the presence of at least one witness may be given in exceptional cases, as provided in the national laws. The word ‘person capable of giving consent’ refers to the legal capacity of the persons giving such consent. It may not refer to the capability of a person to understand the complexities involved in a trial and to take an informed decision.

The Directive also refers to individuals who are incapable of giving informed consent and the process to be followed in taking informed consent\(^{224}\). The Directive upholds the individual rights and freedom by stipulating that the interest of the patient will prevail over the interest of the science and the society, and prohibits any other kinds of inducements other than compensation.

The Regulations\(^{225}\) on protections of individuals with regard the processing of personal data by the community institutions and bodies and on the free movement of such data allows the data subjects to access the data and also have the right to obtain from the controller blocking the data where (a) their accuracy is contested by the data subject, for a period enabling the controller to verify the accuracy, including the completeness, of the data, or; (b) the controller no longer needs them for the accomplishment of its tasks but they have to be maintained for purposes of proof, or; (c) the processing is unlawful and the data subject opposes their erasure and demands their blocking instead.

\(^{223}\) Art.2 (j), M. C. Bassiouni, *supra* note 9.
\(^{224}\) Art.5, M. C. Bassiouni, *supra* note 9.

In the event of no proper informed consent, a clinical trial participant could intimate proceedings to block the processing of the data.

The new Regulations\(^{226}\) states that the co-operation between members states in assessing a request for authorization of a clinical trial should not include aspects of intrinsically national nature, such as informed consent. It also state that no undue influence including that of a financial nature, is exerted on subjects to participate in the clinical trial\(^{227}\). The new Regulation further states that in order to certify that informed consent is given freely, the investigator should take into account all relevant circumstances which might influence the decision of a potential subject to participate in a clinical trial, in particular whether the potential subject belongs to an economically or socially disadvantaged group or is in a situation of institutional or hierarchical dependency that could inappropriately influence her or his decision to participate\(^{228}\).

However it was criticized that the newly adopted regulation introduces special derogations to informed consent, whereby a subject consenting to participate in a clinical trial would be asked in parallel "to consent to the use of his or her data outside the protocol of the clinical trial exclusively for scientific purposes. "Simplified means for informed consent" are also made possible in certain situations\(^{229}\).

EU Directives does not mandate for audio or video recording of the informed consent process. Informed consent is one of the most critical aspects of preventive HIV vaccine trials which require stringent compliance and any dilution on the same could have an adverse impact on the trial participants.

\(^{226}\)M. C. Bassiouni, *supra* note 9 .
\(^{227}\)Art.28(h) R. B. Ghooi, *supra* note 18.
\(^{228}\) R. B. Ghooi, *supra* note 18.
5.2 Clinical Trial Regulatory System in India

India has been a hub of clinical trials and is very significant for clinical trials of HIV Vaccine in view of the considerable number of HIV population in India. India also has distinct categories of population with different social backgrounds, race, ethnicity etc, which may be suitable for a preventive HIV vaccine trial in India.

HIV exhibits considerable genetic variation, and if projections are correct, India will soon have the largest number of HIV infected persons and the importance of a prophylactic vaccine for India cannot be underestimated. The Clinical Trial scenario in India was controversial due to the conduct of illegal trials, though illegal HIV Vaccine trials were not reported in India. Earlier there were controversial trials like the trial of anti-cancer drug, Letrozole, as a fertility drug in India. More than 400 women, who had been trying in vain to conceive, were enrolled without their knowledge or consent to take part in clinical trials across India to see if the drug induced ovulation. The drug, was produced by Mumbai-based generics manufacturer, Sun Pharmaceuticals. The women were under the impression that they were receiving an expensive fertility treatment. The Permission to use Letrozole for breast cancer in older women was given in United States, Britain and other countries after reviewing the results of at least four very large double blind, randomised, placebo controlled clinical trials involving 14,105 female subjects.

There were reports surfaced on the approvals of drugs without testing. Times of India has reported that, just months after the Parliamentary Standing Committee on Health exposed how the country’s highest office on drugs - the

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Central Drugs Standard Control Organization (CDSCO) approved 33 new drugs between January, 2008 and October, 2010 without testing them through trials on Indian patients, between January and July 2012, the CDSCO has approved fourteen new drug molecules of which only nine have undergone clinical trials.

The Parliamentary Standing Committee has submitted a report on the alleged irregularities in conduct of studies using Human Papilloma Vaccine (HPV) in India\textsuperscript{233}.

Earlier in view of the inadequate regulations in India, it was difficult to fix the liability of Sponsors and Clinical Research Organisations (CROs), since they are smart business associates. It would be hard to corner them for violations as they do follow the norms and submit to the regulatory agencies with piles of documentation involving elaborate consent forms signed and accepted by trial subjects. Investigators -the bridges between CROs and patients are the holy grails, claiming to follow rules to the tee\textsuperscript{234}. Though the scenario has changed much recently.

Earlier, ‘economic expedient’ more than “human welfare” was what had shaped Indian government’s policy on clinical trials. What is however, disgusting was the manner in which the misery of Indian people has been leveraged to sell India as the destination of choice for outsourcing clinical trials\textsuperscript{235}. Indians were highly willing (prevalence = 47%) to participate in clinical trials when they were convinced that there were personal healthcare advantages.


It is important to note that although personal health benefit is often thought of as an individual driver of participation, it may often be affected by cultural, socio-economic and healthcare conditions prevailing in a country. Though personal health benefits and altruism were the major influencing factors, monetary gain also emerged as a significant theme. In a developing country like India where poverty is rampant, participating in trials that offer monetary incentives is an extra source of income. Even when the trial does not offer any monetary compensation, the free care and treatment serves as a strong attraction for patients who otherwise cannot afford the cost of treatment.\(^{236}\)

The Government of India had provided fiscal incentives to clinical trial at various times, which includes to exemption of service tax on services of technical testing or analysis of newly developed drugs, including vaccines and herbal remedies on human participants by a clinical research organization approved to conduct clinical trials by the Drug Controller General of India\(^{237}\), import duty exemption for Drugs / materials required for being used in a clinical trial for which permission has been granted by the Licensing Authority under the provisions of the Drugs and Cosmetics Rules, 1945\(^{238}\). However the exemption of service tax was withdrawn and was made taxable with immediate effect in the union budget in 2014\(^{239}\).

In India 100% Foreign Direct Investment (FDI) was allowed in the Pharmaceutical sector for industrial activities, which conceived externally-sponsored research as a form of FDI thus, externally-sponsored research in their


\(^{237}\) Government of India, Ministry of Finance, Department of Revenue, Notification no 12/2012-service tax, March 17, 2012).


territories is actively promoted as a strategic economic policy. India was cited as an example where, externally-sponsored research brought foreign capital and skilled manpower, also offers great opportunities for the transfer of technology to developing countries, and contributes immensely to capacity building for biomedical research in developing countries\textsuperscript{240}.

5.2.1 Statutory Frame work and Policies

In India, \textit{Public Health and Sanitation}\textsuperscript{241} is a subject falling in the state list and ‘Drugs’ are a subject matter falling in the concurrent list\textsuperscript{242}, as both the state and central government has the power to regulate the clinical trials of drugs under the Drugs and Cosmetics Act 1940 and the Drugs and Cosmetics Rules, 1945, as amended from time to time. Schedule Y of the Drugs and Cosmetics Act,1940, and the amended Drugs and Cosmetics Rules, 1945 deals with the rules and regulations and the procedures to be adopted in Clinical Trials. The Indian GCP Guidelines and ICMR Ethical Guidelines for Bio Medical Research on Human Participants lay down the various standards for conduct of the Clinical Trials. Further the prevention of the extension from one state to another of infectious or contagious disease or pests affecting man, animals or plants is in the concurrent list\textsuperscript{243}.

The National Population policy 2000, formulated National Socio- Demographic Goals 2010, aiming to control the spread of AIDS and to promote greater integration between the management of reproductive tract infections (RTI) and sexually transmitted infections (STI) and the National AIDS Control Organisation\textsuperscript{244}.

\textsuperscript{240} R. N.Nwabueze, Legal and Ethical regulation of Bio Medical Research in Developing Countries, 2013, at p.5.
\textsuperscript{241} Entry 6, List II, CONSTITUTION OF INDIA.
\textsuperscript{242} Entry 19, List III, \textit{Id}.
\textsuperscript{243} Entry 29, \textit{Id}.
National AIDS control and prevention policy 2002\textsuperscript{245}, stated its objective to constantly interact with international and bilateral agencies for support and cooperation in the field of research in vaccines, drugs.

The policy initiatives recognize the need to encourage and support research and development and state that the Government will look out for collaborative research with scientific groups in developed countries for development of vaccines suitable for the strains of HIV prevalent in India. Development and trials of each vaccine will be subject to standard ethical guidelines developed and adopted by the Indian Council of Medical Research.

The National Health Policy 2002, emphasise the need for Universal Immunisation against preventable diseases and needs to be assured of an uninterrupted supply of vaccines at an affordable price\textsuperscript{246}. The policy also emphasise the need for health research focused on new therapeutic drugs and vaccines for tropical diseases such as T.B, malaria and also sub types of HIV/AIDS prevalent in the country. The policy also encourages private entrepreneurship in the field of medical research for new molecules / vaccines, inter alia through fiscal incentives\textsuperscript{247}.

However the National Vaccine Policy 2011 emphasise the research and development (R&D) and manufacturing of vaccines for locally prevalent diseases in India, on priority\textsuperscript{248}. It also mentions that the Clinical Trials are very crucial for decision making about vaccine development and the same should be planned and executed according to Good Clinical Practice (GCP) guidelines and maintain highest standard as possible\textsuperscript{249}. Even after more than sixty six years of the independence, the national health policies have not been able to achieve their objective in letter and spirit as they failed to bring social justice and security,

\textsuperscript{246} Para 4.11.1.2, NATIONAL HEALTH POLICY 2002.
\textsuperscript{247} Para 4.15 Id.
\textsuperscript{248} Para 4, NATIONAL VACCINE POLICY 2011.
\textsuperscript{249} Para 4.2.3 Id.
which necessitated the need for a comprehensive legislative frame work to enforce the right to health and healthy life for the public.

The Department of Health Research under the Ministry of Health and Family welfare, Government of India, has formulated a draft National Research policy\textsuperscript{250}, which sets one of its objective, to foster inter-sectoral coordination in health research including all departments within the government, private sector and academia to promote innovation and to encourage production of vaccine etc. The critical ongoing and proposed activities as listed in the Department of Health research in its XII Plan (2012-17) proposals mentioned that research on vaccines would continue on identification of new targets and vaccines, testing of new vaccines and clinical trials on HIV and other pathogens\textsuperscript{251}.

The Health Research Policy 2007\textsuperscript{252} of ICMR considers health research as an investment and is aimed at better coordination among various stake holders in health research. The research policies are general in nature and not specifically addressing research on preventive HIV vaccine. The other national policies addresses the need for development of a vaccine for HIV as well, which reflects the priorities of the country and the urge to develop a vaccine for HIV prevention and control.

The ownership of vaccine developed in India will be a crucial factor in having an affordable vaccine for public health use\textsuperscript{253}. In India, the Ministry of Health and Family welfare had set up a Department of AIDS Control and National AIDS Control Organisation as a part of it. However the Department of Bio Technology


\textsuperscript{253} R. Ramachandran supra note 1 (Vaccine Research in India, , FRONTLINE,15: (26), December 19, 1998- January 01, 1999, available athttp://www.frontline.in/static/html/fl1526/15260840.htm.)
in collaboration with International AIDS Vaccine Initiative (IAVI) has initiated collaborative research on development of a HIV/AIDS vaccine\textsuperscript{254}.

The Medical Council of India Act, 1956, Central Council for Indian Medicines Act, 1970 also regulate the conduct of clinical trials in India. Clinical Trials related to HIV vaccine are also governed by the above laws, and there is no special enactments, neither any rule specifically applicable to the HIV Vaccine Clinical Trials in India. The Central Drugs Standard Control Organisation (CDSCO) is the main regulatory body currently regulating the Clinical Trials in India. Apart from CDSCO, the Ethics Committee also plays a crucial role in the clinical trial approval process.

The Drugs and Cosmetic Rule 1945, defines Clinical Trial\textsuperscript{255}. This definition is more comprehensive than the definition given by WHO and covers both preventive and therapeutic vaccine trials. This definition similar to the definition of clinical trials in Indian GCP Guidelines, except to the extent that the statutory definition is more broad to include all human subjects, whereas the GCP Guidelines mentions about patients / non patient volunteers. The definition under Drugs and Cosmetics Rules does not specify the requirements of voluntariness in case of non patients / healthy individuals, as it is broad enough to cover any human subjects.

In comparison to Russia, Latin America, China or Africa, the speed of regulatory approval in India is relatively rapid. With proper documentation, clinical trial applications can be approved in 8-10 weeks (for drugs marketed in India for more than four years), or may stretch to 12-14 weeks for drugs not approved in India. This is compared with 6-12 months for similar studies in other countries making India more suitable for these studies\textsuperscript{256}. Though there were efforts on the part of

\textsuperscript{255} Rule 122 D AA, DRUGS AND COSMETIC RULES, 1945.  
the government of India to promote clinical research industry, the clinical trials were poorly regulated.

However, in the recent past, India witnessed a change in face of the regulations in medical research industry and there were efforts on the part of the government to strengthen the regulatory frame work in recent times, especially after the filing of a writ petition\textsuperscript{257} before Supreme Court by the NGO, Swasthya Adhikar Manch. The intervention of Hon’ble Supreme Court in one of the Public Interest litigations filed as well as the media interventions has caused drastic changes in Indian Clinical Trial regulatory scenario.

The Ministry of Health and Family welfare has constituted an Expert Committee under the chairmanship of Prof. Ranjit Roy Chaudhary for formulating policies and guidelines for new drugs and clinical trials. The Government has approved the recommendations of the committee and based on this various actions were formulated. Pursuant to the recommendations, it was advised to provide compensation in the event of injury or death to a clinical trial participant in case of drug related anomaly discerning at a later stage and accepted to be drug related\textsuperscript{258}.

CDSCO in a recent circular on placebo controlled trials mentioned that there are no reasons to deprive a patient of a drug in placebo controlled trials. The Pharmaceutical companies, investigators, drug regulators and the Ethical Committees would have to ensure that the design used in placebo controlled clinical trials, is appropriate, efficient and ethical\textsuperscript{259}.

\textsuperscript{257} Swasthya Adhikar Manch v. Ministry of Health and Family Welfare and others, W.P.(C) 33 of 2012, (Supreme court of India).


\textsuperscript{259} CDSCO, Placebo Controlled Trials, Reg, File no 12-01/14DC .Pt.47 , dt .03-07-2014
The cautionary note on placebo controlled trial is relevant for HIV Vaccine trials, in view of the ethical issues and social harm it may cause as the participation might lead to increased risk of HIV infection because the participants will think themselves protected by the vaccination and may increase the risk behavior. The issue related to risk minimization of the subjects is the responsibility of the Ethics Committee, and any research design for placebo controlled trials outlining the risks and benefits involved may also compel the investigators, sponsors to think of any alternative trial designs / protocols. A consultation process which may include the discussions on the possible issues and outcomes, if published will be beneficial to the research community and will be of public interest.

5.2.2 Regulatory System in India and the Procedural Requirements

Clinical Trials in India are to be approved by the Drugs Controller General of India (DCGI) and the Institutional Ethics Committee of the centre where the clinical trial is carried on. The Central Drugs Standard Control Organization (CDSCO) office along with the Indian Council of Medical Research (ICMR) have adopted international regulatory guidelines and issued Indian versions of the same. India launched Pharmacovigilance Program in 2004. ICMR issued the Ethical Guidelines for Biomedical Research on Human Subjects in 2000 and Indian GCP guidelines was released by CDSCO in December 2001. Biological products Guidance for industry issued by CDSCO office and Guidance on common technical document for the New Drug Application (NDA) were other initiatives for the streamlining the requirements for conducting clinical trial and new drug approval process in India.

Post 2000, the Drugs and Cosmetics Act, 1940 was amended several times, which made radical changes in the Clinical Trial industry. The Drugs and Cosmetics Rules 1945 describes on the application for permission to conduct clinical trials for New Drugs / Investigational New Drugs. The Rule mandates

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260 ICMR, ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH ON HUMAN SUBJECTS IN 2000, GCP GUIDELINES, 2001
261 Rule 122 DA, DRUGS AND COSMETICS RULES, 1945
the grant of permission of the Licensing Authority as defined under the Act\textsuperscript{262}. Before granting the permission, the Licensing Authority is required to satisfy the data provided on the clinical trials and the permission granted shall be subject to conditions as stated in Form 45 or 45A, or Form 46 or Form 46 A, as the case may be\textsuperscript{263}. Rule 122 DA mandates that no clinical trial whether for clinical investigation or clinical experimentation by institution shall be conducted except under and in accordance with the permission in writing of the licensing authority.

Rule 122 DAC prescribes that approval of ethics committee shall be obtained before initiation of the study and the clinical trial shall be registered at the Clinical Trial Registry of India (CTRI) before enrolling the first patient for the study. The ethics committee are also required to be registered under the Act. The annual status report of each clinical trial as to whether it is completed or terminated and in case of termination, the detailed reasons for the same shall be communicated to the Licensing authority. This amendment signifies the amount of control exercised by the regulatory authorities in Clinical Trial. Further the rule mandates for conduct of clinical trials in compliance with the approved protocol requirements of schedule Y, and the Good Clinical Practice guidelines for conduct of clinical trials in India. Further the Rule also mandates report of Serious Adverse Events (SAE) occurring during clinical trial, after due analysis, within ten days of occurrence as per Appendix XI and in compliance with Schedule Y.

However the Indian Regulations does not define Adverse Event, though Indian GCP guidelines define Adverse Event. Serious Adverse Event is explained in Schedule Y 5 (A) as amended, as an un toward medical occurrence during clinical trial that is associated with death, in patient hospitalization (in case the study being conducted on out patients), prolongation of hospitalization (in case the study was being conducted on in-patient), persistent or significant disability or incapacity, a congenital anomaly or birth defect or otherwise life threatening.

\textsuperscript{262} Rule 21, DRUGS AND COSMETICS RULES, 1945
\textsuperscript{263} DRUGS AND COSMETICS RULES, 1945.
The definition is in consonance with the definition as mentioned in E6 Good Clinical Practice\textsuperscript{264}.

However the definition as given in Schedule Y has some difference from the definition as referred in the Indian GCP, which includes any adverse event or adverse drug reaction, which may lead to death, in inpatient hospitalization (in case the study being conducted on outpatient), prolongation of hospitalization (in case the study was being conducted on in Patient), persistent or significant disability or incapacity, a congenital anomaly or birth defect or otherwise life threatening. The new rule 122 DAC mandates for compliance of Good Clinical Practice Guidelines for conduct of Clinical Trials in India, it does not specifically prescribes for the reporting of an adverse event or adverse drug reactions. Schedule Y (5)(A) (2) mandates for report of all serious and unexpected adverse events to licensing authority, the sponsor, Ethics Committee within 24 hours of occurrence as per Appendix XI, the wordings used 'serious and unexpected adverse events' may give rise for a strict interpretation, and may compel only reporting of serious and unexpected adverse events instead of all unexpected adverse events and adverse drug reactions irrespective of whether it is qualified to be an SAE or not.

As per the Indian GCP\textsuperscript{265} the Sponsor should establish detailed Standard Operating Procedures (SOP’s). The Sponsor and the Investigator(s) should sign a copy of the Protocol and the SOPs or an alternative document to confirm their agreement. This makes the Sponsor accountable with the Investigator for all the aspects of the trial, including any non compliance by the investigator and other co researchers or employees. The Indian GCP also provides for appointing a Monitor by the sponsor or Contract Research Organisation (CRO) for monitoring and reporting the progress of the trial and for verification of data. The monitor


\textsuperscript{265} ICMR, 3.1.3, INDIAN GOOD CLINICAL PRACTICES
ensures that the trial is conducted, recorded and reported in accordance with the Protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements\textsuperscript{266}.

However it is evident that the appointment of monitor may be only an enabling provision, and shall not dilute the legal liability or responsibility of the sponsor in any manner. The Indian GCP also mentions about Blinding / Masking, which is a method of “control experimentation” in which one or more parties involved are not informed of the treatment being given. Single blind refers to the study subject(s) being unaware, while Double blind refers to the study subject(s) and/or investigator(s), monitor, data analyst(s) are being unaware of the treatment assigned\textsuperscript{267}. Blinding in HIV vaccine trials can create serious legal and ethical issues. How effectively this can be adequately informed and explained to the participants during the informed consent process, given the social, educational and economic background of the participants are concerned.

In cases where the Participants consent to be randomly assigned to vaccine or placebo groups, and to be “blinded” to their status, some participants, however, will be able to determine whether they received the vaccine by seeking an HIV antibody test from an outside source: this is known as “unblinding” oneself. It is hard to predict the effect of unblinding on a vaccine trial. Will participants who discover that they did not receive the vaccine drop out of the study? Will those who learn that they did receive the vaccine take more behavioral risks and thus be at higher risk of infection than the placebo group? If so, could this mask a partially protective vaccine\textsuperscript{268}?: It may be noted that in STEP Study - one of the double blinded study- in HIV vaccine funded by Merck Research Laboratories; the Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID), in the US National Institutes of Health (NIH); and the NIH-sponsored HIV Vaccine Trials Network (HVTN), though addressed the pre-specified primary

\textsuperscript{266}D, Osmond, \textit{Ethical and Legal Issues of Vaccine Clinical Trials}, FOCUS, A Guide to HIV Research and Counseling, Vol 8, No 1, December 1992,
study outcomes, it has challenged the field to more fully understand the role of vector-based immunity, the potential for vaccine-induced increased acquisition, and to mine the wealth of data and specimens in this human trial of a CMI vaccine, to understand the vaccine’s failure. The vaccine contained no HIV and no one could have contracted HIV from the vaccine, but whether the vaccine could have increased anyone’s risk of contracting HIV. There are still many questions left unanswered by the STEP trial. Buchbinder said that the trial participants would need to continue to be followed to find out if the apparent extra vulnerability to HIV conferred by the vaccine was long-lasting.

The question whether the other trial participants should be informed of the occurrence of serious adverse events or adverse events and to be given an opportunity for withdrawal from the clinical trial, though they have the liberty to withdraw from the clinical trial at any time, needs to be addressed.

5.2.3 Research Ethics Committee: Independence, Obligations and Accountability.

Ethics committees are having a critical role in conducting clinical trial. The legislative intention on the scope of the Ethics Committee is for the protection of the subjects as the Ethics Committee has a duty to evaluate the risk to the subjects, expected benefits, adequacy of documentation for ensuring privacy, confidentiality and justice. At present the Drugs and Cosmetics Rules as amended, mandates, registration of Ethics Committee. The Rule mandates that Ethics Committee shall review and accord approval to a clinical trial protocol without prior registration with the Licensing authority as defined in rule 21(b) for registration of ethics committee.

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271 Id.
272 Rule 122 DD, DRUGS AND COSMETICS RULES, 1945.
The Rule also requires that the Licensing Authority shall be informed in writing in case of any change in membership or constitution of Ethics Committee. However the Rule does not mandate for giving any reason for change in constitution or membership of Ethics Committee, which poses a question as to whether the Rules have not foreseen the possibility of membership of Ethics Committee be changed to suit the requirements of the sponsor. The procedure of such registration is to be made by filling an application 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.

The Rule defines Ethics Committee as a committee comprising of medical, scientific, non-medical and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a clinical trial and it shall be responsible for reviewing and approval the protocol, the suitability of the investigators, facilities, methods and adequacy of information to be used for obtaining and documenting informed consent of the study and adequacy of confidentiality safeguards.

The Indian GCP Guidelines defines Ethics Committee as an independent review board or committee comprising of medical / scientific and non-medical / non-scientific members, whose responsibility is to verify the protection of the rights, safety and well-being of human subjects involved in a study. The independent review provides public reassurance by objectively, independently and impartially reviewing and approving the “Protocol”, the suitability of the investigator(s), facilities, methods and material to be used for obtaining and documenting “Informed Consent” of the study subjects and adequacy of confidentiality safeguards.

The composition and scope of Ethics Committee is detailed in Appendix VIII of schedule Y. It also emphasizes that as far as possible based on the requirement

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of research area such as HIV, Genetic disorder, etc., specific patient group may also be represented in the Ethics Committee. However the Drugs and Cosmetics Rules do not mandate that the members of the Ethics Committee should be trained in the Ethics issues concerning Clinical Trials.

The Appendix VIII does not mention about the exit, voluntary withdrawal of members and the rules in respect of the same and is liberal in the SOP to be followed, and policy regarding the training of new and existing committee members and to prevent conflict of interest. Subject experts are also allowed to be called for meeting, but without voting rights. Maintenance of records mandatory at least for five years post completion or termination of the Trial. The format for according approval to clinical trial protocol is also included in Appendix VIII.\textsuperscript{274}

In case of any serious adverse events occurring to the clinical trial subjects during the clinical trial, the Ethics Committee shall analyze and forward its opinion as per procedure specified in Appendix XII of schedule Y. However this does not take into account the adverse drug reactions and adverse events, or any long term impact which may occur post trial. The distinction between serious adverse events, adverse events, adverse drug reactions are required to be noted. The regulatory reporting mandates for reporting of serious adverse events and not simply adverse events or adverse drug reactions. The rules also do not prescribe any reporting standards or classification of reporting. If the principle to be followed is to report any serious adverse events and not all adverse events, the proper analysis of risk involved may not be feasible, though the close monitoring will be done by the Ethics Committee. There is no common data base for the decisions of the Ethics Committee even after taking necessary precautions to safe guard the privacy of individuals and also the confidentiality issues.

\textsuperscript{274} Appendix VIII, SCHEDULE Y, Drugs and Cosmetics Rules, 1945
The participation of subjects in HIV Vaccine Clinical Trial will have a risk on the subjects and as it is tried on healthy individuals, there will be more risk than benefit from an individual perspective. It is also not clear as to what would be the decision of Ethics committee if the participant is more exposed to risk than benefits from an individual perspective. Whether he is entitled for a compensation from the sponsor, even if he gets HIV due to his risk behavior which may be even fuelled by his participation in the HIV Vaccine trials. Sponsor has a duty to compensate for a trial related injury. If a trial related injury is not visible till the conclusion of the trial, especially in case of HIV, where the window period\textsuperscript{275} for HIV virus will be 11 days to three months for various tests and the gestation period of the virus may take years and the State has a duty to compensate him. However some of the trial participants may have HIV antibodies even if they are not infected with the virus. HIV-1 Vaccines have the potential of confounding interpretation of HIV tests because of the antibody induced by vaccination\textsuperscript{276}. This can even create difficulties in getting a health or life insurance for the trial participants. It may not be easy for any Ethics Committee to mitigate such risks faced by the trial participants of HIV preventive vaccine clinical trials.

The Community Advisory Boards (CAB) play an important role in facilitating ethical conduct of clinical trials, which may also increase the acceptability of the trial.

The Community Advisory Board composed of local workers and community representatives, should liaise between researchers and the community; advice on study procedure, consent and data forms in order to protect the community;


play a significant role in community information and education, and help in recruitment and retention of study participants\textsuperscript{277}.

Given the conservative attitude of the Indian society, achieving the desired outcome in an HIV vaccine trial could be still a challenge.

5.2.4 Impartiality of Ethics Committee

The Ethics Committees are faced with daunting challenges such as, reluctance of individuals to serve on these committees, infrequent meetings, heavy workload, inadequate space and lack of administrative support. These constraints not only lead to delays in approvals but also force most of the ECs to restrict their activities to initial appraisal and approval of study protocol and documents, review of reported serious adverse events and examination of the periodic and final report submitted by the investigators\textsuperscript{278}. Ethics Committees, ethical guidelines and norms, and independent review boards are all different ways of ensuring compliance with established ethical guidelines and good practices. Ethics committees cannot conduct their task responsibly, unless they get the data needed to evaluate ethical behavior. Evaluating conflict of interest, addressing cultural specificities in obtaining informed consent from vulnerable population are some of the critical issues.

A subject’s ability to independently determine risk and the availability of guaranteed medical care during trials might obscure his/her desire to do a meaningful risk-benefit assessment before providing informed consent. Punitive measures and/or legal liability may help in the implementation of the ethical guideline in trials. Training of ethics committee members, accreditation of these


committees and the development of stringent guidelines with detailed operating procedures are necessary279.

As per the Requirements and guidelines for registration of Ethics Committee280 there should be no conflict of interest, but it does not define or mention what is conflict of interest in the context of clinical trials. The Ethical Guidelines for Biomedical Research on Human Participants issued by ICMR281 describes Conflict of Interest (COI) as a set of conditions in which professional judgment concerning a primary interest like patient’s welfare or the validity of research tends to be or appears to be unduly influenced by a secondary interest like non-financial (personal, academic or political) or financial gain. Academic institutions conducting research in alliance with industries/ commercial companies require a strong review to probe possible conflicts of interest between scientific responsibilities of researchers and business interests (e.g. ownership or part-ownership of a company developing a new product)282. The issue is that, if a Employee stock option is offered in a company conducting Clinical Trial, whether it will be considered as a conflict of interest. The full disclosure may assist in managing the conflict of interest but the ways to mitigate without denying the legitimate entitlements of investigator or other clinical research associates would be a much bigger challenge.

Even the ICMR guidelines has given much discretionery rights to the Institutional Review Boards / Committees to take a decision in this regard and also suggested that Institutions and IECs need self-regulatory processes to monitor prevent and resolve such conflicts of interest. The IEC can determine the conditions for management of such conflicts in its SOP manual. ICMR Guidelines for preparing Standard Operating Procedures (SOP) for Institutional Ethics Committee for

280 Appendix VIII, DRUGS AND COSMETICS RULES, 1945, supra note 30.
282 Id
Human Research does not suggest the conditions or ways to manage such Conflicts of Interests. Any undisclosed conflict of interest can expose the investigators, sponsors and other entities to a risk and the issue will be whether the party who knew of the conflict had a legal obligation to intervene to prevent the research from proceeding on the basis of the conflict. The existence of an undisclosed conflict of interest can also adversely affect the informed consent process.

It is also mentioned that Prospective participants in research should also be informed of the sponsorship of research, so that they can be aware of the potential for conflicts of interest and commercial aspects of the research. Those who have also to be informed of the secondary interest in financial terms should include the institution, IEC, audience when presenting papers and should be mentioned when publishing in popular media or scientific journals. Whether the participants will have capability to understand the issues related to conflict of interest is a doubtful question. Further the proceedings of Ethics Committee and the discussions are confidential. As such it is unlikely that a clinical trial participant will be aware as to how the conflict of interest was mitigated.

The members shall voluntarily withdraw from Ethics Committee meeting while making a decision on application which evokes a conflict of interest which may be indicated in writing to the Chairman prior to the review and recorded so in the minutes. It also mandates that all members shall sign a declaration on conflict of interest. There is no formal training on bioethics mandated for EC members. The fear of a perceived nexus between sponsor/CRO and EC prevents sponsor/CRO sponsored training for EC members. In India, being an EC member is hardly ever a full-time job; so, resources for training are also limited. There is no clarity on the quantum of remuneration to be paid to the Ethics Committee and who shall

\[283\] L.H. Lund and K. Swedberg, supra note 52.

be responsible for payment of the same. Normally the sponsor is required to bear the expenses. However the issue is whether this will be a major conflict of interest especially when the appointing authority and remunerator are one and the same. Another issue is whether an Ethics Committee takes a decision which has an adverse impact on the financial interest of the sponsor or CRO from a practical perspective and how they will be able to protect the interest of the subjects when there is such a conflict of interest.

Some research ethics committees operate within research institutions (where they may be known by different names, including “institutional Research ethics committees review board” (IRB)), while others operate on a regional or national basis. The advantage of research ethics committees that operate within research institutions is that they are familiar with the local conditions and can engage in closer monitoring of ongoing studies. The disadvantage is that the committee may feel inhibited from rejecting or requesting significant changes to studies, given the institution’s financial interest in attracting externally funded research projects. Regional and national committees are further remote from the site where the research is conducted, but they may provide greater consistency and have greater legitimacy in the eyes of the research community and the public285.

The basic responsibility of an Institutional Ethics Committee (IEC) is to ensure a competent review of all ethical aspects of the project proposals received by it in an objective manner. IECs should provide advice to the researchers on all aspects of the welfare and safety of the research participants after ensuring the scientific soundness of the proposed research through appropriate Scientific Review Committee. In institutions where this is lacking, the IEC may take up the dual responsibility of review of both, the scientific content and ethical aspects of the proposal286.

286L. H. Lund and K. Swedberg, supra note 52.
Earlier it was reported that the Ethics committees meant to protect the rights of patients enrolled in clinical trials are doing roaring business in the name of reviewing, approving and monitoring—especially the so-called independent ethics committees (IEC). It was also alleged that in most cases, no one seems to know what exactly are these entities that proclaim themselves to be independent ethics committees; who owns them and who collects the revenue earned; how is it distributed and to whom, and how do they decide what amount to charge\(^{287}\).

The recent amendments to the Drugs and Cosmetics Rules have improved the scenario to a limited extent, but there are still unresolved issues. It appears that there is a need for the regulatory authorities to regulate the appointments and remuneration of Ethics Committee in view of the public interest as well as the participants interest involved in the Clinical Trial.

As per the GCP Guidelines, the sponsor and/or investigator should seek the opinion of an independent Ethics Committee regarding suitability of the Protocol, methods and documents to be used in recruitment of Subjects and obtaining their Informed Consent including adequacy of the information being provided to the Subjects. The Ethics Committees should do regular monitoring for the compliance of the Ethics of the approved programmes till the same are completed. Such an ongoing review is in accordance with the Declaration of Helsinki and all the international guidelines for biomedical research\(^{288}\).

In the light of new guidelines issued by the CDSCO on the audio and video recording of the informed consent process, the guidelines issued by ICMR, the extent of liability of Ethics Committee needs to be evaluated. It is unclear as to whether the sponsor will be responsible for the negligence, or neglect on the part of ethics committee who approves the trial, given their independent status is concerned. The members of Ethics Committee being independent may not have any employer-employee relationship with the sponsor of the trial; as such the


\(^{288}\) ICMR, GCP Guidelines
sponsor may not be vicariously liable for the acts of the members of the ethics committee. However, each member of ethics committee is separately and individually responsible for any harm suffered by a research subject as a result of the negligent review of a protocol.

The Ethics Committee is not a separate legal entity. Its members can have individual or collective liabilities depending on the nature of decisions they may take. The concept of individual liability however calls for appropriate standard of care. As the Ethics committee has a multidisciplinary composition, different standard of care should be applied to determine the liability of members of ethics committee. The standard of care applicable to professional or scientific members shall not apply to determine the liability of lay or community representatives. The risk exposure to a member of ethics committee could be the tortious liability based on the common law principles related to negligence or duty of care etc. The SOP issued by ICMR for Ethics committee mentions that the Ethics Committee should consists of 5-15 members from different departments and the quorum should be minimum five members. There is no mandate that the scientific or medical expert in the relevant field should mandatorily be present in order to constitute the quorum. In that scenario, any liability arising from the decision of Ethics committee comprising of a quorum will expose even a lay or community representative to liability under tort. Appendix VIII of drugs and cosmetics rules mentions that the ethics committee should be minimum five members with representations from basic medical scientist, clinician, legal expert, social scientist and also lay person from the community. Further the guideline also mentions that Ethics committee shall have the option to call subject experts for advice, which is one of the risk mitigation options for a non expert who is a member of such ethics committee.

The independence of Ethics Committee is crucial for a fair ethical decision making. At present there is no professional body to certify, train and regulate the members of the ethics committee, though the respective professional bodies

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which they belong can play a role. However other than Doctors including Dentists, Nurses, Pharmacists, and Advocates, the other professionals who are members may not be even controlled by any professional bodies. Periodical audit of the proceedings of ethics committee are to be made mandatory to ensure sufficient check on the Ethics Committee.

Though there are various guidelines and operating procedures available for the functioning of the ethics committee, it carries lot of discretionary powers, with regard to analyzing the risk involved in the research design, risk to trial participants etc, without any supervision on it in the absence of any complaints. At present there is no uniform criterion with regard to the remuneration payable to Ethics Committee. It will bring more transparency in the system and also may attract more professionals if uniform criteria can be adopted for the remuneration of ethics committee especially in view of the fact that it is unlikely to be a permanent or full time job.

Indian Council of Medical Research has issued a Guideline for preparing Standard Operating Procedure for Institutional Ethics Committee for Human Research, with an objective to contribute to the effective functioning of the Institutional Ethics Committee (IEC), as prescribed by the Ethical Guidelines for Biomedical Research on human subjects of ICMR.

The recent changes in the regulations mainly due to the intervention of the Hon'ble Supreme Court in pending Public interest litigation 290 is note worthy. This case has made a significant impact on the clinical trial scenario in India and accelerated the changes in the regulatory scenario for monitoring and the compliance of the regulations and guidelines at Clinical Trial sites. DCGI has issued a circular to all its zonal offices for monitoring clinical trials and also for constituting expert committee to conduct clinical trial inspection at least once in a year to ensure that there are compliance of clinical trial sites by the investigators.

290 Weinschecn, supra note 14.
172 Directorate General of Health Services, Office of Drugs Controller General ( India), (New Drugs Division), F.No 12-01/09-DC-(Pt-32) , w.e.f 15 Jun 2009
as per the schedule Y of Drugs and Cosmetics Act, GCP guidelines, and other regulatory requirements.

5.2.5 Clinical Trial Registry – Public Policy and Transparency issues

Public policy changes for improvement, accountability and transparency of clinical trials practice across the globe has also brought significant changes in India. Transparency is one of the most important principles of scientific research. It is necessary for achieving the goals of science and for enabling society to benefit from the results of research\textsuperscript{291}. Registration of Clinical Trials before the ICMR Clinical Trial registry was made mandatory in India\textsuperscript{292}. The reasons that led to the establishment of clinical trial registry is linked with the international initiatives in this regard, which includes, the initiative of World Health Organization, to establish an International Clinical Trial Registry platform, with a view to make the clinical trial data more transparent and publically available and the decision of the International Committee of Medical Journal Editors (ICMJE) that no trials will be considered for publication, from 1 July 2005, unless they are included on a clinical trials registry\textsuperscript{293}, besides the widespread averments of publication bias. Investigators’ and editors’ inclination to publish only those trials that have proved the new intervention to be better than standard therapy is one of the reasons for several trials with so-called 'negative results’ remaining unpublished\textsuperscript{294}.

The main objectives of the registry are to establish a public record system by registering all clinical trials on health products that are drugs, devices, vaccines and herbal drugs. Further, it also aims to create a more complete, authentic,


public and readily available data of all ongoing and completed clinical trials and to provide a corrective system against "positive result bias" and "selective reporting" of research results to peer review publication. In addition, the vision is to increase awareness and accountability of all the participants of the clinical trials and also for public access to promote training, assistance and advocacy for clinical trials by creating database and modules of study for various aspects of clinical trials and their registration.\textsuperscript{295}

Though trial registration was voluntary and was a moral responsibility of the researcher, it was mandatory in India with effect from 15\textsuperscript{th} June 2009.\textsuperscript{296} The traditional approach of confidentiality of clinical trial data has changed to a great extent bringing mandatory disclosure requirement. The Clinical Trial Registry of India (CTRI) requires disclosure of all 20 items of WHO Trial Registration data set and further additional disclosure requirements which are CTRI specific.\textsuperscript{297} The CTRI data set fulfils the requirements of the WHO ICTRP and the ICMJE, and includes additional elements aimed at aiding the valid design, ethical conduct and eventual reporting of clinical trials.\textsuperscript{298} The Indian disclosure requirement is much more comprehensive than that was mandated by WHO. This is more beneficial in HIV Vaccine Trials, where the risk exposure to healthy individuals is more in view of the gravity of the disease. There could be conflict of interest between the business interests of the CROs and sponsors and public interest. Public interest could outweigh the commercial interest in case of HIV Vaccine Trials as HIV Vaccine is something which the world is eagerly looking for.

\textsuperscript{295} A. Pandey et al., \textit{Clinical Trial Registry- India : Redefining the conduct of Clinical Trials}, 45,\textit{INDIAN JOURNAL OF CANCER}, 79-84, 2008.
\textsuperscript{297} CTRI, Data Set and Description, available at http://ctri.nic.in/Clinicaltrials/CTRI_Dataset_and_Description.pdf, (Last visited on January 15, 2015).
The trial registration may not be a complete solution to the issues related to delayed disclosure or incomplete disclosure of trial data results. It is unclear as to how the accuracy of the registration data that is not peer viewed, scientific validity of statistical analysis and interpretation could be validated using the existing registries or resources. In India, the Right to information Act, 2005 is a tool, which can be used to access the clinical trial data. However in *Ms.Deepa Venkatachalam v. Ministry Of Health And Family affairs*, the Hon'ble Chief Information Commission (CCI) observed that the Clinical trial reports cannot be furnished without severing the information which deals with patient related data in order to protect the privacy and confidentiality of the individual.

However the Hon'ble CIC has ordered that the respondents shall provide the information to the Appellant using the provisions of section 10(1) of the RTI Act 2005, severing all and any patient related information as also any information which deals with the exclusive intellectual property rights of the pharmaceutical companies. What will be the exclusive IPR of the Pharmaceutical companies is a doubtful question. It is necessary to have clear guidelines with regard to segregation of the portion of the data which can be disclosed to public and which cannot be disclosed.

In India, there is no statutory definition of confidential information, and is governed by the law of contracts. The proposed draft of National Innovations Act 2008, defines confidential information. The definition of the proposed draft was liberal in the sense that it protects, the information, including formula, pattern, compilation, program, device, method technique or process that is not readily available or accessible to persons within the circles that normally deals

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with the kind of information in question, those that are secrets simply because it is having commercial value.

In USA, the Freedom of Information Act\textsuperscript{302}, provides Exemption 4, which permits non disclosure of agency records, if such records contain “commercial or financial information that was obtained from a person and is privileged or confidential. The Clinical trial data qualify as commercial information under this exemption and will be withheld if they are deemed confidential; that is, if disclosure would “cause substantial harm to the competitive position of the person from whom the information was obtained. In Public Citizen Health Research Group v. Food and Drug Administration et al\textsuperscript{303}, the plaintiffs sought both preclinical and clinical studies for all drug applications that had been discontinued due to death or serious injury of patients or due to safety concerns arising from preclinical studies. In reversing the order for release of the information, the Court of Appeals for the District of Columbia Circuit acknowledged that the plaintiff’s desire to “review whether the FDA is adequately safeguarding the health of people who participate in drug trials” satisfied the central purpose doctrine because it directly revealed “what the government is up to. However, the court firmly rejected the public interest in preventing “other drug companies from repeating [the drug sponsor's] mistakes, thereby avoiding risk to human health as an improper derivative use, stating that it is not open to the plaintiff, to bolster the case for disclosure by claiming an additional public benefit that is not related to 'what the government is up to\textsuperscript{304}.

The issue is the degree of protection to be given to the confidential information, disclosure of which may cause commercial injury to the sponsor of the clinical


trial or Contract Research Organizations. The participant details cannot be
disclosed in view of the privacy issues and this may not be of public interest. It is
a debatable issue, whether to notify the spouse on the participation of clinical trial
or any adverse events or serious adverse events to the participant during the
trial.

5.2.6 Informed Consent and Voluntariness

The issues related to informed consent had always been a debatable issue and
an area of concern in India, in view of the social, educational and economic back
ground of the participants of clinical trial. Their ability to understand the long term
issues, medical jargons and medical complications that may arise out of the
participation was always doubtful, even if it is assumed that they have high risk
appetite.

Informed consent requirements in medical research are at much higher level than
the consent requirements under the Indian Contract Act 1872\textsuperscript{305}, which will put
the trial participants in equal footing that of the investigator before entering into
the contract for participating in the clinical trial. The Individual autonomy and
freedom of choice of the participant is more important in the clinical trials.

The Indian Penal Code, 1860,\textsuperscript{306} stipulates that an act done in good faith for
benefit of a person under 12 years of age or of un-sound mind by consent either
express or implied by the guardian or other person having lawful charge is not an
offence by reason of any harm. The aforesaid exception is not available if there is
an intention to cause death or grievous hurt. The Code further stipulates that a
consent given under fear of injury or mis-conception of fact would not be a valid
consent under the Code\textsuperscript{307}. Every consent involves submission, but it by no
means follows that a mere submission involves consent. Mere submission by
one, who does not know the nature of act done, cannot be consent\textsuperscript{308}. Though

\textsuperscript{305} Sec 13, Indian Contract Act 1872.
\textsuperscript{306} Sec 89, INDIAN PENAL CODE.
\textsuperscript{307} Sec 90, Indian Penal Code ,
\textsuperscript{308} R VsLock (1872) LR 2 CCR 10, 14.
the code exonerates the culpability of a physician in case of medical emergency, the participation in a Clinical Trial is not due to a medical emergency, but normally will be a calculated decision.

The code of ethics issued by Indian Medical Council\textsuperscript{309} permits the physician to undertake clinical drug trial or other research involving patients or volunteers as per the guidelines of ICMR, and violation of the ICMR guidelines in this regard shall constitute misconduct. The code also specifies that the consent taken from the patient for trial of drug or therapy which is not as per the guidelines shall also be construed as misconduct. The Code also stipulates that\textsuperscript{310} any complaint with regard to professional misconduct can be brought before the appropriate Medical Council for Disciplinary action. If upon enquiry and after hearing the registered medical practitioner, if the medical practitioner is found to be guilty of committing professional misconduct, the appropriate Medical Council may award such punishment as deemed necessary or may direct the removal altogether or for a specified period, from the register of the name of the delinquent registered practitioner. However there is no clarity or guideline regarding the quantum of punishment which can be awarded in the event of violation of ICMR guidelines\textsuperscript{311} in connection with the research or consent taken from the participants.

The ICMR guidelines stipulates on the informed consent process that it protects the individual’s freedom of choice and respect for individual’s autonomy and is given voluntarily to participate in research or not. It also mentions that adequate information about the research is given in a simple and easily understandable unambiguous language in a document known as the Informed Consent Form with Participant/ Patient Information Sheet. The latter should have following components as may be applicable:

\textsuperscript{309}Id.


\textsuperscript{310} Clause 8.2 and 8.3 , ibid

\textsuperscript{311} L. H. Lund and K. Swedberg, supra note 52.
1. Nature and purpose of study stating it as research
2. Duration of participation with number of participants
3. Procedures to be followed
4. Investigations, if any, to be performed
5. Foreseeable risks and discomforts adequately described and whether project involves more than minimal risk
6. Benefits to participant, community or medical profession as may be applicable
7. Policy on compensation
8. Availability of medical treatment for such injuries or risk management
9. Alternative treatments if available

The guidelines are in consonance with the international guidelines in this regard. The Indian GCP Guidelines\textsuperscript{312} describes Informed consent as the ‘voluntary written assent of a subject’s willingness to participate in a particular study and in its documentation. The confirmation is sought only after information about the trial including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available and of the subject’s rights and responsibilities has been provided to the potential subject.

Limitations to the doctrine of informed consent do exist, and physicians do not have a duty to disclose every remote risk associated with a medical procedure. For example, the physician does not need to disclose the chance that a spinal anesthetic may be contaminated and may therefore cause neurologic damage if the chance of contamination is no longer considered a current risk. Nor do physicians have a duty to disclose risks that are considered common knowledge.

or already obvious to the patient, such as the risk of infection following a surgical operation.\textsuperscript{313}

However what is considered to be common knowledge or already obvious to the participant of a clinical trial is difficult to understand, it also depends on the educational level and social background of the participants. The guidelines issued by the Indian regulatory authorities for audio and video recording of the informed consent process is a welcome step in safeguarding the interest of the research participants, however it is not clear as to the extent of enforcement in this regard.

The draft guidelines prescribes the essential elements of information to be provided to the research participants while recording the consent\textsuperscript{314} in a language that is non-technical and understandable by the study subjects and directs that the same shall be recorded through audio-visual means. Since the guidelines also mandates strict confidentiality, subsequent verification of the compliance may be possible only by the ethics committee or by the regulatory authorities.

The draft guidelines\textsuperscript{315} also insists for the description of any reasonably foreseeable risks or discomforts to the subject and description of any benefits to the subject or others reasonably expected from research. It further insists that if no benefit is expected subject should be made aware of this. However a participant of a HIV preventive vaccine clinical trial may not personally benefit by the participation in the trial as he being a healthy individual and risk which he may be exposed will be very high in view of the likely hood of getting infected.

The issues related to the voluntariness of consent often arises in situation where the individuals consent to participate in research could potentially result from


\textsuperscript{314}Order --F.No GCT/20/SC/Clin./2013 DCGI, Office of Drugs Controller General (India), dt 19 Nov 2013.

\textsuperscript{315}Id
coercion or duress\textsuperscript{316}. The National Health Bill 2009, defines\textsuperscript{317} ‘capacity to consent’ means ability of an individual, including a minor or a person with mental disability, assessed by the relevant health service provider on an objective basis, to understand and appreciate the nature and consequences of a proposed health care or of a proposed disclosure of health related information, and to make an informed decision concerning such health care or disclosure. However the Government of India has clarified that it has no plans to introduce National Health Bill\textsuperscript{318}.

5.2.7 Trial related Injury and Compensation

In case of any such participants, getting infected during his participation in the clinical trials, the main issue will be whether this will be a trial related injury or not. The healthy individual of a preventive HIV vaccine trial may be likely to get infected, due to his own actions / high risk behaviour which may even include unprotected sex, which is neither controlled by the investigator nor by the contract research organisation.

Though this will be a true test of the efficiency of the vaccine, the question is

- whether in such cases if a trial participant is infected with HIV due to his own high risk behaviour, will be protected and compensated by the sponsor / contract research organisation,
- whether any such HIV infection will be treated as a trial related injury,
- Whether such participants are entitled for lifelong follow up treatment.

One should also bear in mind, the participation in a preventive HIV vaccine trial will give the subject immense confidence to indulge in high risk behaviour including unprotected sex, which may expose them to several other sexually

\textsuperscript{316}S.Loue, Legal And Ethical Aspects of HIV Related Research, 1995, p.30.
transmitted diseases including HIV. Whether the fact that the participant was already in the high risk group is a sufficient reason to deny any of the legitimate claims of the trial participant is debatable.

Clinical trial using placebo in HIV preventive vaccines could have a serious adverse impact on the trial participant, who is already in the high risk group, as the participants may believe that they were given vaccine, though the truth could be otherwise. As per CDSCO, any health care professional, Doctors including Dentists, Nurses and Pharmacists can report any adverse events in the prescribed form, making the regulatory requirements flexible to trigger the action of voluntary reporting to the pharmacovigilance centres. There is also provision to maintain confidentiality and the report will not amount to an admission that the medical personnel, manufacturer, or the product has contributed to the event\textsuperscript{319}.

The Rule\textsuperscript{320} mandates that, in case of an injury occurring to the clinical trial subject, he or she shall be given free medical management as long as required. In case of the injury occurring to the clinical trial, such subject shall also be entitled for financial compensation and it shall be over and above any expenses incurred on the medical management of the subject. In case of clinical trial related death his nominees are entitled for financial compensation as ordered by the Licensing Authority, which shall be over and above the medical management expenses. The expenses of medical management and financial compensation in case of clinical trial related injury or death of the trial participant shall be borne by the sponsor of the clinical trial. In case of HIV, the medical management required will be lifelong and how to ensure the payment of expenses for a long term is doubtful in the absence of any common fund collected from sponsors which can be utilised for payments in case of any non payment by the sponsor due to various reasons like closure of business, liquidation, wilful default etc.

\textsuperscript{320} Rule 122 DAB, DRUGS AND COSMETICS RULES, 1945.
The compensation formula adopted on the basis of two risk factors,

- Age of the subject,
- Risk factor depending on the seriousness and severity of the disease, presence of co morbidity and duration of the disease of the subject at the time of enrolment in the clinical trial.

However, in case of patients whose expected mortality is 90% or more within 30 days, a fixed amount of Rs. 2 lacs should be given. Thus, it will be seen that the compensation amount will vary from a minimum of Rs.4 lacs to a maximum of Rs.73.60 lacs depending on the age of the deceased and the risk factor.

The compensation for death or trial related injury of the subject may be an incentive for many of trial participants of the clinical trials, especially due to the exclusion of pre-existing diseases by the insurance companies. However the same is unlikely to be an incentive or motivation for a healthy individual to participate in the Preventive HIV vaccine trials.

The specific issues related to HIV such as social stigma, discrimination etc is not taken into consideration for the computation of compensation. Aspects of individual sacrifice and risk taken for the benefit of the community by participating in the vaccine trial and the state responsibility to protect the subjects also are important factors to be considered.

5.2.8 State Responsibility to Protect the Trial Participants of HIV Vaccine Trials

The direct individual benefits from participation in a research for HIV preventive vaccine is marginal as it can only be done on a healthy individual. The risks are more including known, unknown, and the risk of contracting HIV through voluntary and avoidable risk behavior, though there will be regular counseling for reducing the risk behavior.
Community involvement in research activities has emerged as one important and necessary strategy for advancing HIV prevention efforts, but defining “community involvement” and implementing it successfully often present numerous challenges. Community involvement may give rise to a wide spectrum of social and ethical questions, especially when the concerned communities include people who are disadvantaged because of ethnicity, income, gender, class or sexuality.\textsuperscript{321}

‘Directive Principles of State Policy’ under the Constitution enumerate guiding principles for States to be followed while formulating their policies. These provide that, it is the primary duty of State to improve public health, and it should promote a social order in which justice: social, economic and political shall form part of all institutions of national life.\textsuperscript{322}

The Regulations does not specifically cast any obligations on the State with regard to the protection of Clinical Trial participants. The obligations to provide medical management and compensation to trial related injury lies with the sponsor of the trial.

In the absence of any statutory mandate, except the protection available under Article 21 of the Constitution, any future possibility of any State responsibility to protect the trial participants should not be considered as an inducement for the participant. The issue is the distinction between legitimate motivation and inducement for participation in the HIV Vaccine Trials.

In view of the nature of the AIDS epidemic, there is a growing public interest in favour of the HIV vaccine as it can change one of the severe health challenges faced by mankind. As such, the participant of any HIV preventive vaccine clinical trial, can be considered as a person doing great service to the mankind. In return,


\textsuperscript{322} Art.38, CONSTITUTION OF INDIA.
there is nothing wrong if somebody argues that there is a state responsibility to protect the research participants against all kind of risks they may face in connection with their participation in the clinical trial.

The Ethical Guidelines available states that the Individuals or communities should not be pressured to participate in a study. However, it is hard to draw the line between exerting pressure or offering inappropriate inducements and creating legitimate motivation. The benefits of a study, such as increased or new knowledge, are proper inducements. However, when people or communities lack basic health services or money, the prospect of being rewarded by goods, services or cash payments can induce participation. To determine the ethical propriety of such inducements, they must be assessed in the light of the traditions of the culture. Risks involved in participation should be acceptable to subjects even in the absence of inducement. It is acceptable to repay incurred expenses, such as for travel. Similarly, promises of compensation and care for damage, injury or loss of income should not be considered inducements\(^\text{323}\).

A study has shown that the willingness to participate in HIV Vaccine trial is also influenced by the risk behaviour of the participant, many of the participants who were in the category of men sex with men (MSM) were willing to participate as they felt it as a contribution to the society and also to protect their families from HIV infection\(^\text{324}\). India being a conservative society, with diversified culture and social attitude, a healthy individual may face lot of challenges for participating in a HIV preventive vaccine clinical trials, especially in view of the risk involved for the health and life of the individual which may include those related to the clinical trial and attributable to the risk behaviour of the individual. In view of the above, a


protection against trial related injury alone will not be of much help to a participant of HIV preventive vaccine trials.

Though the researchers generally do counselling for the participants to reduce the risk behaviour, still it may be difficult to change the behaviour. Any injury which may be attributable to the risk behaviour may not be considered as a trial related injury. Any injury or death of the subject occurring in clinical trial due to the following reasons shall be considered as trial related injury or death and the subject or their nominee is entitled for financial compensation.\textsuperscript{325}

(a) Adverse effect of investigational product(s) (IP);
(b) Violation of the approved protocol, scientific misconduct or negligence by the sponsor or his representative or the investigator;
(c) Failure of IP to provide intended therapeutic effect;
(d) Use of placebo in a placebo-controlled trial;
(e) Adverse effects due to concomitant medication excluding standard care, necessitated as part of approved protocol;
(f) For injury to a child in-utero because of the participation of parent in a clinical trial;
(g) Any clinical trial procedures involved in the study.

The Drugs and Cosmetics Rules do not define ‘\textit{scientific misconduct}'. A comprehensive definition of scientific misconduct can be traced in the documents of United States Public Health Service (USPHS)\textsuperscript{326} as the “Fabrication, falsification, or plagiarism, in proposing, performing, or reviewing research, or in reporting research results.

It includes:

\textsuperscript{325} Rule 122 DAB, DRUGS AND COSMETICS RULES, 1945.
• fabrication is making up data or results and recording or reporting them;
• Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record;
• Plagiarism is the appropriation of another person’s ideas, processes, results, or words without giving appropriate credit.

Manipulation, falsification and fabrication of data, records may amount to scientific misconduct. Since the risk behaviour of the participant which is extremely private, sometimes it may be difficult to conclusively decide whether the participant was infected due to his risk behaviour or participation in the trial.

Scientific Misconduct needs to be distinguished from fraud. Scientific misconduct/fraud is a violation of the standard codes of scholarly conduct and ethical behavior in scientific research. Reasons for fraud/misconduct in clinical Research could vary from personal to professional. Fraud could be a result of professional over ambition to become famous, a gain in prestige by being a part of international clinical trials or for financial interests. At times it could be due to laziness of the researcher or site staff for complex studies needing repeat assessments.327

The Epidemic Diseases Act, 1897 empowers the state and the central governments to prescribe regulations on any dangerous epidemic disease. However there is no definition of dangerous epidemic disease provided in the Act, leaving lot of discretion to the governments. The Goa Public Health (Amendment) Act, too, by implication, allows for disclosure/notification to public officials of an individual’s HIV status by giving them the power to test and isolate such persons they suspect of having the virus.

However the physical physiological and mental health condition of a person is falling in the ambit of sensitive personal data or information\textsuperscript{328}. The rule further mandates a body corporate to provide policy for privacy and disclosure of information and also provides for disclosure of such personal data or information shall be with the prior permission of the provider of such sensitive information, unless such disclosure is agreed by contract between the provider and the body corporate, or necessitated for compliance of a legal obligation\textsuperscript{329}.

The Rules framed under the Information Technology Act, 2000, mandates the obligation to protect the sensitive personal data or information on the body corporate, however it is not clear as to whether it will be applicable where the disclosure is made before any individual medical practitioner, who may not fall in the ambit of ‘body corporate’\textsuperscript{330} under the Act.

Though clinical trial is conducted by the body corporate only, the possibility of misuse of any loop holes in law cannot be ruled out. The Rules\textsuperscript{331} mentions on disclosure of such sensitive personal data or information if provided under the contract. In the context of a HIV clinical Trial participant, the parties are unlikely to be on an equal bargaining position and limited disclosure is essential for the purpose of research, failing which the very purpose of research may be defeated. The Rules will assist in unnecessary public disclosure, which is required for maintaining the confidentiality and privacy of the subjects.

A few earlier judgements on HIV were not in favour of the person affected with HIV. In Smt. Lucy D’ Souza v. State of Goa\textsuperscript{332} was one of the first litigations on the issue of HIV/AIDS in India. S. 53(1) (vii) of the Goa Public Health Act, 1987, empowered the government to isolate a person suffering with AIDS. The Act did not specify a particular period of isolation or where it should take place, but that

\textsuperscript{328} Rule 3, INFORMATION TECHNOLOGY (REASONABLE SECURITY PRACTICES AND PROCEDURES AND SENSITIVE PERSONAL DATA OR INFORMATION) RULES 2011.
\textsuperscript{329} Rule4, Rule 6,CIOMS, supra note 322.
\textsuperscript{330} Sec 43 A, Information Technology Act, 2000.
\textsuperscript{331} Z. Chu, supra note 323.
\textsuperscript{332} AIR 1990 Bombay 355 ( High Court, Bombay )
isolation was acceptable for such person, and at such institution or ward as may be prescribed. Thus wide powers were given to the government to take away the liberty of the individual on grounds that a person was suffering from AIDS.

The Constitution guarantees right to life, and the right to life includes right to health and healthy living. The expression 'life' assured in Art.21 of the Constitution does not connote mere animal existence or continued drudgery through life. It has a much wider meaning which includes right to livelihood, better standard of life, hygienic conditions in work place and leisure. No one shall be arbitrarily deprived of his right to life. The state has a duty to prevent activities which may result in arbitrary deaths and also to reduce threats to human life such as malnutrition and infectious disease. As such state is bound to initiate steps to facilitate clinical trial for HIV preventive vaccine, and also ensure sufficient standard of care for the trial participants. In Municipal Council, Ratlam, v. Shri Vardhichand and others, the Hon'ble Justice Krishalyer observed that the state will realize that Art. 47 make it a paramount principle of governance that steps are taken for the improvement of public health as amongst its primary duties.

The 'right to health' is a fundamental right of the workmen. The Court also held that this right is not only available against the State and its instrumentalities but even private industries to ensure to the workmen to provide facilities and opportunities for health and vigour of the workman assured in the provision of Part IV of the Constitution which are 'integral part of right to equality under Art 14 and right to invigorated life under Article 21 which are fundamental rights to the workmen.

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333 Consumer Education and Resource Centre Vs Union of India, AIR 1995, SC 922 ( Supreme Court of India )
334 AIR 180 SC, 1622 ( Supreme Court of India)
335 Kirloskar Brothers Ltd v. Employees' State Insurance Corporation (1996) 2 SCC 682. ( Supreme Court of India )
However the participant of a clinical trial is not a workman as there is no employer employee relationships between the participant and sponsor, investigator or CROs. The present law covers lifelong medical management in case of trial related injury. However it does not prescribe for mandatory follow up for a prescribed period for especially in case of participation in trials related to HIV vaccine, which can create health complications as well.

India does not have any mandatory partner notification laws with regard to infectious diseases. The Supreme Court in one case\textsuperscript{336} where there is an allegation of breach of privacy and confidentiality wherein the Hospital on discovery of petitioner as HIV positive, informed his fiancée about this condition because of which the marriage was called off and his community ostracized him. The Court observed that the relationship between doctor and patient was that of trust. No information acquired during course of treatment should be divulged without the prior permission of the patient. In case of HIV/AIDS patients, confidentiality is paramount because of repercussions of disclosure. Nevertheless, an HIV infected person has a right to lead a normal life but not at the cost of others. In the instant case the right of health of Petitioner’s fiancée was pitched against his right to privacy. Supreme Court held that when two rights collide the one that promotes morality and public interest should be upheld. The hospital’s act was to protect the life of another person therefore, they could not be held liable for consequences of their act. The Supreme Court said that in fact the Respondent’s silence would have made them \textit{particeps criminis} i.e. partners in crime.

In another case\textsuperscript{337} the Apex court held that, the timely disclosure of the HIV positive status of the patient to his fiancée saved her from being contracted with HIV and hence the disclosure did not invade the right to privacy. These judgments are relevant in the context of HIV preventive vaccine clinical trial.

\textsuperscript{336}Mr.X v. Hospital Y, AIR 2003, SC 664 (Supreme Court of India)

\textsuperscript{337}Dr.Tokugha Yepthomi v. Appollo Hospital Enterprises Ltd, AIR 1999, SC 495 (Supreme Court of India)
Trial participant may have antibodies in his body, which may show as HIV positive, though he is not actually HIV positive.

Participation in a HIV vaccine clinical trial by a healthy individual is a service to humanity and is in the interest of the society. In that event it should be a mandatory obligation on the part of the state to protect the interests of the participants rather than going by the ratio of the judgments of Hon’ble Supreme court upholding public interest where there is a conflict with privacy. However the present legal frame work may not address the issues related to partner notification / disclosure of the health of the trial participants.

HIV-1 vaccines have the potential of confounding interpretation of HIV tests because of the antibody induced by vaccination. Depending on the HIV associated sequences used in the candidate vaccine, not only may the screening enzyme immunoassay (EIA) be reactive but the Western Blot may also be difficult to interpret$^{338}$. Testing for vaccine induced sero positivity (VISP) at the end of the study and providing participants with their VISP status is critically important to prevent social harms, incorrect HIV diagnosis, and inaccurate reporting to health agencies.

A misinterpretation of VISP can be minimized by clinicians obtaining a complete patient history (eg, participation in an HIV vaccine trial) and interpretation of the Western Blot and HIV RNA by Polymerase Chain Reaction. However, given the added time and cost associated with obtaining this information, clinicians may overlook or not pursue this information$^{339}$. In the light of the Supreme Court judgments on the issues related to privacy and public interest, these issues will be more significant. The disclosures may expose the participants to undesirable social conditions, especially in rural India, though there is significant change in

$^{338}$E.K. Quirk et al., _HIV sero conversion without infection after receipt of adenovirus- vectored HIV type 1 vaccine_. Clinical Infectious Disease. 2008 available at: http://cid.oxfordjournals.org/content/47/12/1593.full, (Last visited on August 9, 2014).

attitude in the recent past. Some countries in the middle east do not allow entry of HIV positive persons and this could also pause a challenge before the trial participants, who may be faced with incorrect diagnosis due to vaccine induced seropositivity (VISp), there by seriously prejudicing his right to life, live with dignity as the present system does not offer any special protection to the participants of preventive vaccine clinical trials.

The Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome (Prevention and Control) Bill, 2014 was introduced in Rajya Sabha in Feb 2014, which prohibits discrimination against persons with HIV and AIDS, provides for informed consent and confidentiality with regard to their treatment, places obligations on establishments to safeguard their rights, and creates mechanisms for redressing their complaints. The Bill lists the various grounds on which discrimination against HIV positive persons and those living with them is prohibited. These include the *denial, termination, discontinuation or unfair treatment with regard to:*

- employment,
- educational establishments,
- health care services,
- residing or renting property,
- standing for public or private office, and
- provision of insurance (unless based on actuarial studies).

The requirement for HIV testing as a pre-requisite for obtaining employment or accessing health care or education is also prohibited. The bill once becomes law will address many social issues faced by the persons infected with HIV, including the unfavorable situations created by the judgments of the Hon’ble supreme court.

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It was reported that the health ministry has finalized\textsuperscript{341} Bio Medical Research on Human Subjects Promotion and Regulation Bill in the wake of the report of the Parliamentary Committee on Health, failing the government and the Indian Council of Medical Research for failing to prevent deaths of adolescent tribal girls in Andhra Pradesh and Gujarat during post-marketing surveillance of anticervical cancer HPV vaccine.

The bill is aimed at protecting the safety and rights of humans used in scientific research. Seeking to set up a Biomedical Research Authority, the proposed law will ensure compulsory registration and evaluation of ethics committees set up in all kinds of research institutions and will have penal provisions for unauthorised research and unethical practices. It will also cover institutions and sponsors undertaking unethical biomedical research at places with inadequate facilities. The Authority will register, monitor and evaluate the performance of ethics committees; evolve performance appraisal systems, and norms and mechanisms for enforcing accountability and transparency; and assess the need for providing protection to vulnerable sections. There is a provision for establishing a “Research Related Injury Relief Fund” from which compensation will be paid. The Bill entitles a child in the womb to claim compensation for any research-related injury, caused in utero by the participation of its mother\textsuperscript{342}.

The regulatory scenario in India has changed post filing of the Public interest litigation by Swasthya Adhikar Manch\textsuperscript{343} before the Supreme Court of India. The Hon’ble Supreme Court by an interim order ordered that until further orders, clinical trials of new chemical entity shall be conducted strictly in accordance with the procedure prescribed in schedule Y of the Drugs and cosmetics Act, 1940, under the direct supervision of the Secretary, Ministry of Health and Family


\textsuperscript{342}A. Dhar ,Bill to make biomedical, health research ethical, THE HINDU, available athttp://www.thehindu.com/todays-paper/tp-national/bill-to-make-biomedical-health-research-ethical/article5143738.ece, (Last visited on April 15, 2014).

\textsuperscript{343}Swasthya Adhikar Manch v. Union of India, W.P. (c) 33 of 12, Supreme Court of India.
Welfare, Government of India. In order to supervise the clinical trial, the ministry has constituted an Apex Committee and a Technical Committee. The Technical Committee will meet every month to oversee the conduct of clinical trials and give its recommendations to the Apex Committee for taking appropriate action. In order to strengthen the review process on application of global clinical trials including clinical trial of New Chemical Entities (NCEs) other than IND, the Ministry of Health and Family welfare has constituted New Drug Advisory Committees (NDACs) of different therapeutic categories. Further, it was also directed that all the Global Clinical Trials (GCTs) /New Clinical Trials (NCEs) should be evaluated having regard to three parameters, namely (i) assessment of risk versus benefits to the patients, (ii) innovations vis a vis existing therapeutic options and (iii) unmet medical need in the country.

The Ethics Committee is not free from limitations. The rules does not prescribe any specific training or qualification in ‘medical ethics’, for becoming a member of ethics committee. Ethics Committee also may not be free from bias. The chances that a member of ethics committee may favor or act according to the interests of the appointing authorities cannot be ruled out, though the present rule mandates that the chairman of the ethics committee should be from outside the institution.

At present the decisions of ethics committee are not subject to any judicial review. As such, who will judge the ethics committee or evaluate their decisions in the absence of any compliant or dispute is a relevant question, in the context of non accessibility of the proceedings of Ethics Committee in view of confidentiality issues. The Drugs and Cosmetics Rules prescribe the qualification\textsuperscript{344} for the members of ethics committee. However it does not stipulate the liability of the members of a research ethics committee, and there is no law or rule which specifically excludes the liability of ethics committee. There should be stringent regulations to ensure the independence of ethics committee, with penal provisions in case of violations.

\textsuperscript{344} SCHEDULE Y, DRUGS AND COSMETICS RULES, 1945
Further there could be still possibilities that research protocol rejected by one ethics committee may be approved by another ethics committee, or reconsidered, reviewed and approved by a reconstituted ethics committee. Due to confidentiality issues, public do not have access to the proceedings of the ethics committee. However, if it is mandatory made available to public even after masking the identity / personal details of the trial participants, any decision of the ethics committee which is not in the best interest of the trial participants can be challenged or put to the notice of the regulatory authorities for timely actions.

5.2.9 CROs, their obligations and responsibilities

The Indian GCP Guidelines defines ‘Monitor’ as a person appointed by the Sponsor or Contract Research Organizations (CRO) for monitoring and reporting the progress of the trial and for verification of data. The monitor ensures that the trial is conducted, recorded and reported in accordance with the Protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements. The CROs may perform sponsor’s trial related duties and assume liability in respect of the trial as per the clinical trial agreement between sponsor and the CROs. However the Drugs and Cosmetics Act, and rules do not absolve the sponsor from any trial related liabilities. The Drugs and Cosmetics Act, 1945 makes the person in charge also liable for the offences including the Company when a company is accused of any offence.

However, the proviso to Section 34 of the Drugs and Cosmetics Act, 1945 absolves the liability of a person if he is able to prove that the offence was committed without his knowledge, and he has exercised all due diligence to prevent the commission of the offence. Section 34 provides that, where an offence under the Act is

345ICMR, GCP GUIDELINES.
committed by the Company, the person in charge of and responsible for the conduct of its business is to be held guilty and be liable to should be proceeded against, should be proceeded against with a view to fix culpability where the offence is committed by a company.\textsuperscript{346} The criminal liability of the CRO is coextensive with that of the Sponsor, however, the Sponsor shall have a defense in view of the provision to section 34 of the Act and the appointment of Ethics Committee and the contract with the CRO for the conduct of clinical trial will be of assistance in case of prosecution. Generally the agreement between the CRO and the Sponsor will be that of Principal to Principal, which may assist the sponsor against many liabilities. The GCP guidelines cast obligations of monitoring the trial.

The Services provided by a CRO may include

- Developing protocols for a clinical trial
- Hosting and managing the sites where the trial is conducted
- Research and study of trial data
- Establishing the principal investigator for trial
- To meet the regulatory requirements for the sponsor as per the agreement
- Arrange the research sites
- To maintain quality of the trial

Though the investigators recruited are required to be adequately compensated, any offer of stake in the success of the products or in the forms of Employees stock options can create a subsequent conflict of interest, as the independent research mind of an investigator could be compromised due to such offers. This is relevant in view of the fiduciary relationship between the doctor and patients in India.

\textsuperscript{346}Murairilal Arora v. State of H.P, 2010(95) AIC 648 (H.P. HC)
CROs can play an effective role in preventing scientific misconduct and maintaining data quality. The obligations of CRO is significant in the context of follow up treatment in case of HIV vaccine trial candidates. Researchers holding clinical trials of HIV vaccine candidates face a great deal of uncertainty in their work. In the process of conducting early-stage vaccine research using a product of unknown efficacy, they are working with study populations in which some participants will inevitably become naturally infected with HIV during the course of the trial.

Thus, decisions must be made regarding the provision of care to research subjects infected with HIV. Additionally, treatment of HIV/AIDS encompasses more than purchasing and supplying medications. Frequent follow-up and monitoring of patients are required due to the high prevalence of side effects from HAART and the inevitable development of drug resistance. The question of "appropriate treatment" gives rise to heated debates over highly sensitive issues.

Because many clinical trials for HIV candidate vaccines are performed in developing countries, one of the main fears is of the creation of a "double standard" for developed and developing countries as a result of funding and infrastructure capacities. Those observing the progress and protocols of clinical trials may ask if appropriate treatment in a rural African community can be equated to appropriate treatment in a major U.S. city.

Clinical trials conducted in America or Europe would require that infected participants receive the best available care, a lifetime regimen of anti-retroviral drugs, but for similar trials held in developing countries, the prospect of such care is dim at present. In 2003, the HIV Vaccine Trials Network (HVTN),


encompassing a collaboration of scientists from 28 research sites, announced that participants who become infected during HVTN trials will receive long-term antiretroviral treatment. Some factors involved in this decision include the belief that provision of ARVs is now feasible in many locations and that providing treatment may aid research by assuring parity between participants at all stages of the trials.  

There is a need for a common fund to be set up by the Government of India for the follow up treatment of the subjects of HIV vaccine clinical trial, in the event of sponsor / CROs fail to provide the lifelong medical management as envisaged under the Act due to many reasons including closure of business / liquidation. In view of the gravity of the epidemic and the shortened life expectancy of the affected patients in the present scenario, it is not in the best interest of the trial participant to litigate and wait for enforcing his legitimate rights for treatment and compensation.

Need for a common fund to be set up by the state to address the issues faced by trial participants, due to compliance issues by Sponsors ,CROs , which may be due to close of business and liquidation as well as there is no guarantee that the expenses towards compliance of obligation towards the trial participants will get priority over other debts or dues . Even the Companies Act, 1956 does not specifically address these types of priority issues.

5.2.10 Investigator – Responsibilities and liabilities

The Indian GCP guidelines defines Principal Investigator, Investigator and Co investigator. The Principal investigator is defined as the Investigator who has the responsibility to co-ordinate between the different Investigators involved in a


study at one site or different sites in case of a multi-centre study. Investigator is defined as a person responsible for the conduct of the study at the trial site. Investigator is responsible for the rights, health and welfare of the study subjects. In case the study is conducted by a team of investigators at the study site then the designated leader of the team should be the Principal Investigator. The Co-investigator person is a person who is legally qualified to be an investigator, to whom the Investigator delegates a part of his responsibilities. The Drugs and Cosmetics Rules stipulates that a qualified physician (or dentist, when appropriate) who is an investigator or sub investigator for the trial should be responsible for all trial related medical (or dental) decisions. It is further stipulated that the Investigator(s) shall be responsible for the conduct of the trial according to the protocol and the GCP Guidelines and also for compliance as per the undertaking given in Appendix VII.

Standard operating procedures are required to be documented by the Investigators for the tasks performed by them. During and following a subject’s participation in a trial, the investigator should ensure that adequate medical care is provided to the participant for any adverse events. Investigator(s) shall report all serious and unexpected adverse events to the Sponsor within 24 hours and to the Ethics Committee that accorded approval to the study protocol within 7 working days of their occurrence. The 24 hours-time line for reporting may be considered as in the interest of the trial subject. However there requires some clarity on the definition of serious adverse events as it mandates reporting within 24 hours.

As per the definition, prolongation of hospitalisation is one of the criteria and includes inpatient hospitalisation if the study being conducted as outpatient, making it mandatory to report even adverse events as well, if it is unexpected. It is also doubtful whether in all cases a correlation can be made with a possible drug reaction or any other circumstances which may lead to hospitalisation.

350 ICMR, GCP GUIDELINES, 351 SCHEDULE Y, DRUGS AND COSMETICS RULES, 1945
rules does not define adverse events, but the GCP guidelines defines adverse events, adverse drug reactions etc.

The conduct of the research in a most ethical manner in compliance of the statutory obligations lies with the investigator. These obligations and his key role in the clinical trial cast lot of risk exposure on him. The legal defence in some of the cases will be covered by the agreement between sponsor and the investigator and other staff who are involved in the conduct of clinical trial, by way of indemnity. It is imperative that the Investigators must carefully read and understand the contract agreement.\(^{352}\)

A physician is a in *fiduciary relationship* with his patients. In India doctors can be a trusted source of recruitment of Clinical trial subjects as the patients generally trust their physicians. When a physician turns to be a clinical trial investigator there will be a change in relationship between him and his patients or the trial participants. This may be in conflict with the traditional doctor patient relationship, as it is doubtful whether the participants of clinical trial in India, who are generally from the socially, educationally and financially backward sections, will be able to identify the distinction between the role of investigator and physician while participating in the trial.

Investigators act to generate scientific knowledge that potentially will result in future therapeutic benefits. Practitioners are focused on the present health and welfare of patients. Notwithstanding the distinction between researcher and clinical practitioner, research can be designed primarily to yield scientific knowledge, such as phase 1 clinical trial, or may offer some direct medical benefit to subjects, such as some phase 3 clinical trials. In each, risks and potential benefits must be weighed and informed consent is to be obtained from prospective subjects, after disclosure of all material information. Since subjects

might misconceive the nature of a research project, particular attention must be paid when researchers offer some medical benefit that can be integrated easily into a course of treatment\textsuperscript{353}.

There is a distinction between the standard of care of a physician and the standard of care to be given to the participants of a clinical trial. While a doctor may consider his main responsibility as doing no harm to the patient and helping them, a clinical investigator is expected to work on the merits and outcome of the clinical trial.

An investigator on breach of duty or violation of research protocol or ethical obligations, resulting in a trial related injury may expose him to offences of causing hurt or grievous hurt under the Indian Penal code\textsuperscript{354}. Absence of mens rea can be a defense in these cases, but any willful violation of statutory obligations for conducting the trial can attribute knowledge of the risk involved and causing hurt may also expose the investigator to criminal liability under the IPC, besides the exposure for violation of the Drugs and Cosmetics Act, 1940. Besides these when it is proved that there is a breach of duty, the investigator may be exposed to claims under tort, for damages, though the present laws does not provide any compensation to participants for participation in a clinical trial which is illegal, in the absence of a any trial related injury.

The informed consent might be compromised even further when the physician/investigator who is responsible for enrolling participants in the trial and obtaining their consent stands to gain financially from each participant who is enrolled. The physician/investigator may be less inclined to emphasize how the experimental treatment differs from the care that is ordinarily provided, the additional risks involved, or lack of direct benefit to the participant\textsuperscript{355}. With regard to the


\textsuperscript{354} SEC 320, INDIAN PENAL CODE .

\textsuperscript{355}72\textsuperscript{nd} REPORT ON THE ALLEGED IRREGULARITIES IN CONDUCT OF STUDIES USING HPV IN INDIA, supra note 4.
standard of care, the criteria fixed under Helsinki Declaration is required to be followed, which clearly states that the benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.\textsuperscript{356}

A physician turned investigator may also face ethical dilemmas especially when there is an uncertainty with regard to the results of the trial. The concept of ‘\textit{equipoise}, the ‘uncertainty principle\textquotedblright, has been represented as a central ethical principle of human experimentation. Equipoise holds that a patient may be enrolled ethically into a randomized controlled trial (RCT) only when substantial uncertainty surrounds which of the trial treatments would most likely benefit them.

It is also advocated that Equipoise is a false and diverting principle, and should be replaced by ‘positive expected value’ using the patient’s values, with elimination of the internal contradictions that surround the concept of equipoise and with a return to the Belmont principles.\textsuperscript{357} The issues related to therapeutic misconception and equipoise may be less applicable in a preventive HIV vaccine clinical trial as it is carried on healthy individuals and the participants are not expected to personally benefit by participating in the trials. The duty of investigator emanates from the statutory frame work which in applicable in India.

Ethical Committees also play a critical role in protection of the subjects. The Schedule Y stipulates that ‘adequate medical care’ is to be given to the participants for any adverse events. What will be the adequate medical care will depend on case to case basis and is open for wide interpretation. If a beneficial interpretation can be adopted this may be sufficient to protect the trial participants.

\textsuperscript{356}PARA 29, HELSINKI DECLARATION.
5.2.11 Strict Liability or Absolute Liability for Trial related Injuries

A trial related injury can occur, due to various reasons, which may include negligence, breach of duty on the part of investigator, ethics committee, failure to maintain adequate standard of care, drug related issues like adverse drug reactions etc, which may give rise to a claim by the trial participants. While certain injuries may be anticipated, and are the inherent risks of the trial, certain others could be avoidable risks. The Drugs and Cosmetics Rule mandates provision of compensation in case of trial related injuries, and treatment for any such injuries as long as is required.

According to Winfield

“Negligence as a tort is the breach of a legal duty to take care which results in damage, undesired by the defendant to the plaintiff”.

The cardinal principle of liability is that the party complained of should owe to the party complaining a duty to take care, and the party complaining should be able to prove that he has suffered damages in consequence of a breach of that duty.

In case where a bus driver was stabbed to death by some miscreants during a communal riots, while he was going to join duty. On the issue of negligence on the part of the employer in not taking adequate precautions for the safety of the diseased, the High Court, Madhya Pradesh, after referring to various English cases observed that

358 DRUGS AND COSMETIC RULES, 1945, supra note 319.
359 As cited in Madhya Pradesh Road Transport Corporation v. BasantiBai 1971 ACJ 328 (M.P.,High Court).
361 supra note 359.
Per Justice G.P. Singh,

"From all these considerations, we are of opinion that in the facts and circumstances of this case, there existed a duty-situation and the management of the C.P.T.S. was liable in negligence in not taking adequate precautions for the safety of the deceased, either by making arrangement for his protection while he was on his way to join his work, or by closing the business temporarily, if no such arrangement for the protection of the deceased was possible."

In a clinical trial, the investigator, and ethics committee owes a duty to take adequate precautions to safe guard the safety of the subjects, failing which subjects may be entitled for compensation.

In, Hedley Byrne and Co. Ltd v. Heller and Partners Ltd362 is a classic case on negligent misstatement. The issue was, under what conditions a person can recover damages for loss suffered by reason of his having relied on an innocent but negligent misrepresentation.

Per Lord Morris of Borth-y-Gest

“If someone possessed of a special skill undertakes, quite irrespective of contract, to apply that skill for the assistance of another person who relies upon such skill, a duty of care will arise. The fact that the service is to be given by means of or by the instrumentality of words can make no difference. Furthermore, if in a sphere in which a person is so placed that others could reasonably rely upon his judgment or his skill or upon his ability to make careful inquiry, a person takes it upon himself to give information or advice to, or allows his information or advice to be passed on to, another person who, as he knows or should know, will place reliance upon it, then a duty of care will arise”

362 (1964) A.C 465 (House of Lords), available afhttp://www.bailii.org/uk/cases/UKHL/1932/100.html, (Last visited on December 15, 2014)
The principles laid down in this case is applicable to Preventive HIV Vaccine Clinical Trials, as the subjects are solely relying on the expertise of ethics committee and investigators in analysing and understanding the risk involved in participation of the trial and they owe a duty of care to the subjects, breach of which can give rise to claims under common law principles.

In *J. Rylands v.T.Fletcher*\(^{363}\) which enunciated the strict liability principle, their lordships, Lord Chancellor and Lord Cranworth concurred with the opinion of Justice Blackburn in delivering the opinion of the Exchequer Chamber.

*Per* Justice Blackburn

> *If a person brings, or accumulates, on his land anything which, if it should escape, may cause damage to his neighbour, he does so at his peril. If it does escape, and cause damage, he is responsible, however careful he may have been, and whatever precautions he may have taken to prevent the damage*.

There are some exceptions\(^{364}\) carved out to the rule in Rylands v Fletcher, which includes consent of the plaintiff and common benefit, which may have relevance in HIV vaccine trial.

As observed by the Delhi High Court\(^{365}\),

*Per* Justice Markandeya Katju,

> This repudiation of the principle in Rylands v. Fletcher is contrary to the modern judicial philosophy of social justice. The injustice may clearly be illustrated by the case of Pearson v. North Western Gas Board, (1968) 2 All ER 669. In that case the plaintiff was seriously injured and her husband killed by an explosion of gas, which also destroyed their home. Her action


\(^{364}\) Delhi Jal Board v.Rajkumar and others, LPA 2451 of 2005, AIR 2006 Delhi 75 ( Delhi HC )

\(^{365}\) Id.
in Court failed, in view of the decision in Dunne v. North Western Gas Board (1964 (2) QB 806) (supra). Thus the decline of the rule in Rylands v. Fletcher left the individual injured by the activities of industrial society virtually without adequate protection.

In India the landmark Constitution Bench decision of the Supreme Court in M.C. Mehta v. Union of India366, which carved out the principle of absolute liability, which is not subject to any of the exceptions to the rule in Rylands v. Fletcher. As observed by the court if the enterprise is permitted to carry on any hazardous or inherently dangerous activity for its profit, the law must presume that such permission is conditional on the enterprise absorbing the cost of any accident arising on account of such hazardous or inherently dangerous activity as an appropriate item of its overheads.

HIV Vaccine Clinical Trial can be considered as a dangerous activity so far as the subjects are concerned in view of the risks involved. The principle of absolute liability can be applied to preventive HIV Vaccine Clinical Trials, which requires the sponsor to compensate for any trial related death, injury. Though the guidelines have been given with regard to the compensation, its considered as inadequate.

The participants injured in an HIV Vaccine Trial will have civil remedies available to them for recovering any compensation, and also may approach the criminal courts in the event of any scientific misconduct or malpractices, which may amount to cheating, or causing hurt to the participants, initiating the criminal remedies in addition to the civil remedies.

This also emphasis the need for protection for the investigators and Ethics committee against undue harassment or dragging them to unwarranted criminal cases. Though a regulatory check in the nature of sanction as may be required for prosecuting the public servants also can be considered to prevent undue

366 AIR 1987 SC 1086 (Supreme Court of India)
harassment, by way of statutory amendment, it may amount to creating a roadblock for the remedies available to the subjects, who are generally under privileged.

5.2.12 Drugs and Cosmetics (Amendment) Bill, 2015

The Bill in its draft form, as published gives a broad definition of Clinical Trial, and also defines ‘new drug’ to include vaccines\textsuperscript{367}. The proposed amendment could bring significant changes in the clinical research industry. The inclusive definition as proposed in the definition of sponsor is to extent the liability beyond a contract research organization, which is normally responsible for the conduct of the Clinical trial.

The definition of sponsor includes individuals, juristic persons, and academic institutions, which may be a non corporate or unincorporated entity, who is responsible for the initiation, financing and management of the clinical trial. The inclusive definition of sponsor as proposed, could make the risk management processes to safe guard the sponsor through a contract research organisation extremely difficult. But the enforceability of any possible action against a sponsor may be difficulty unless he has a place of business in India.

The Bill prescribes imprisonment and penalty for violation of the provisions of the Act with regard to the conduct of clinical trials except with the permission granted by the Central Licensing Authority as prescribed under the Act and proposes punishment for conducting a clinical trial without the approval of the ethics committee\textsuperscript{368}. The issue as to whether a death or disability of a trial participant is caused by the clinical trial or not will be decided as prescribed under the Act.

A penalty\textsuperscript{369} is also prescribed for failure of the sponsor to provide compensation or medical treatment as prescribed under the Act. The Bill also casts responsibility on the sponsor as well as the person or body corporate permitted

\textsuperscript{367} Cl.3, Drugs and Cosmetics (Amendment ) Bill 2015, 3, 5, Draft published on 31 December 2014,

\textsuperscript{368} Cl. 4K, Id.

\textsuperscript{369} Cl.4Q, Id.
under section 4 A to provide compensation under the Act. Though the proposed amendments lays down the responsibilities of the ethics committee clearer, it also clothes the Ethics Committee with more powers, allowing it to revoke any previous approvals granted after writing to the sponsor and central licensing authority. The Central Licensing Authority has the right to suspend or cancel the registration granted to an Ethics Committee, review all the approval granted by the Ethics Committee for continuance or otherwise of the clinical trial, when the Central Licensing Authority is satisfied that the central Licensing Authority is not satisfied that the Ethics Committee is unable to discharge its functions and responsibilities under the Act. The members of a suspended or cancelled Ethics Committee shall be disqualified to be a member of another ethics committee for two years. This shows the collective responsibility casts on the Ethics Committee. However it is not clear whether any member who has descended or absent during the decision of the Ethics Committee which triggered the action leading to disqualification could escape disqualification. The proposed amendment does not mention on the requirement of a personal hearing before initiating an action for disqualification.

The Bill provides more powers for inspection by the Drugs Control Officer or any other officer authorised by the Licensing authority. They will have the power to inspect the facilities, record, data, documents, book, drugs etc and to seek clarifications with regard to the information and record regarding clinical trial or matters relating thereto. The proposed amendment also allows initiation of prosecution by a person aggrieved and by any consumer association\(^\text{370}\). A trial participant of an HIV vaccine trial will be a person aggrieved, however the NGOs working for HIV patients or HIV vaccine clinical trial participants, cannot be whereas consumer association are allowed.

The Clause 4T of the Bill does not prevent prosecution under any other law for the

\(^{370}\) Cf. 4K, Drugs and Cosmetics (Amendment) Bill 2015, Draft published on 31 December 2014.
time being in force for any act or omission which constitute an offence under chapter 1 A as proposed in the Bill. This will make the investigators and sponsors more vulnerable to legal proceedings under different laws viz possible actions under the Indian Penal Code. Since the prosecution can be launched by many persons under the Act, including a person aggrieved, it is quite possible that different proceedings on the same set facts can be initiated by different persons under Drugs and Cosmetics Act, 1940, and Indian Penal Code. It can also be argued that different proceedings under the same set of facts may attract the provision of Art.20 (3) of the Constitution on double jeopardy or Section 300 Cr.P.C, or section 71 of IPC.

However as observed by the Supreme Court\textsuperscript{371}, Per Justice Dr.B.S.Chauhan “the test to ascertain whether the two offences are the same is not identity of the allegations but the identity of the ingredients of the offence. Motive for committing offence cannot be termed as ingredients of offences to determine the issue”.

The proposed Bill does not provide for appeal against the decisions of Ethics Committee, or liability of members or previous members of a reconstituted Ethics Committee. It also does not discuss about transfer of the research review / overseeing by one Ethics Committee to another etc.

\textsuperscript{371}Sangeetaben Patel V. State of Gujarat ( 2012 )7 SCC 621