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## Globalization of Clinical Trials- A Review of Underlying Ethical and Scientific Considerations Involving Human Subjects in India

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**Abstract** The conduct of clinical research involving the participation of human beings embroils a variety of ethical issues like dignity, liberty, autonomy, privacy and bodily integrity. The ethical conduct of a clinical trial just not only includes a signature on the informed consent form by the concerned participant but protecting the dignity, rights, interests, and safety of research subjects must continue throughout the duration of the study. Pharmaceutical industries are legally and ethically bound to protect human participants involved in clinical research. This article reviews and describes the scientific and ethical aspects of clinical trials and necessary regulatory mechanism to protect the rights, dignity, and privacy of human subjects: the institutional review board, the Ethical committee, the sponsor, the informed consent process and the investigator in developing countries like India. This article also reviews some of the important issues like informed consent, payment for participation in a clinical trial, and defining standard of care in critically ill patients.

**Keywords** *Ethical Committee, Pharmaceutical Industries*

### 1. Introduction

Globalization is the process of interchange of different views, products, ideas, services and culture across the boundaries resulting in international integration. Globalization has wide impacts on societies across the world. In a definition of Globalization given by Lee “all the spheres of human interaction including social, political, economic, environmental eroding the boundaries of all kinds come under globalization” [8].

Globalization on one hand has resulted in greater economic growth, prosperity, cost savings and short timeline for clinical testing, but on the other hand critics point to the exploitation of subjects, risk to their health and emergence of economic disparities particularly when clinical trials are conducted in low- and middle- income countries. Globalization has proved to be a boon for biomedical and pharmaceutical companies in terms of their business.

In 2009 Glickman *et al* in his study “Ethical and scientific implications of globalization of clinical research” raised important questions about the economical and ethical issues of clinical research. Findings of the study show that approximately one third of the trials (157 of 509) are conducted outside United States and a majority of study sites (13521 of 24206) are outside United States in developing countries. In the report developing country trials are labeled as scientifically questionable and morally inappropriate [12]. The study concluded that genetic and other population differences could render results that did not apply to the target population [12]. The report also raised concerns that money was paid in recruiting poor volunteers. He explained reasons for this dramatic shift that pharmaceutical companies realize cost savings and shorten timeline and less regulatory barriers in developing countries for clinical testing [12].

In a study Ethical issues in tuberculosis vaccine trials conducted in 2000 by Dixie E. Snider certain ethical issues like generic issues against tuberculosis in involving human subjects in developing countries were raised [3]. The results of study show that there was exploitation of trial subjects for testing interventions in developing countries [3].

An article in New England Journal of Medicine in 19 February says that the twenty largest U.S. - based pharmaceutical industries conduct about one third of their phase III clinical trials outside the country and a majority of their study sites also are outside United States. Article says that two decades ago, nearly all of these clinical trials were done in the U.S. The number of trials in developing countries has grown 8% a year since 1997, according to Food and Drug Administration data [7].

In a study in 2010 “Clinical Research ethics in developing countries: challenges and the way forward” Dr. Ballari Brahmachari and Dr. Arun Bhatt concluded that the trend of globalization in clinical research is increasing with more and more sponsors in economically advanced countries outsourcing trials to developing nations. According to this study the reasons behind this is less cost in conducting trials and a large pool of patients for any disease ensuring rapid recruitment and lesser timelines for completing clinical trials [18].

According to a survey done by Journal of medical ethics in February 2004 less than six out of 10 trial protocols are reviewed by an ethical committee. In China only one out of 10 trial protocols are reviewed [7].

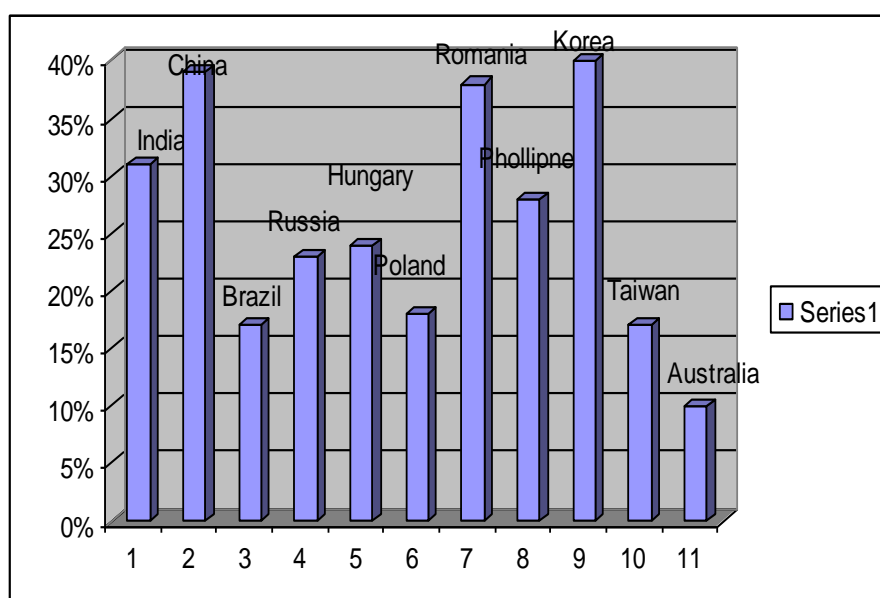
Biomedical research is conducted for collecting and analyzing data from which conclusions are drawn that help in improving the care of currently unknown beneficiaries in the future. Human participants are the important sources of data in this regard. This phenomenon raises important questions about the moral, social, economic and ethical issues of clinical research. Recently in conducting clinical trials more emphasis is laid on monitoring welfare of participating subjects during the conduct of research. Just taking an informed consent form does not account for the moral, social and ethical concerns in conducting clinical trials. Safety, rights and interests of the human subjects for clinical trials should be ensured and continued throughout the duration of study. This article describes and defines the underlying reasons for globalization of clinical trials, bring out the important moral, ethical and behavioral concerns associated with the globalization of clinical research, the monitoring regulatory bodies to ensure the adequate protection of the dignity, rights and welfare of participating human subjects and review of responsibilities of the regulatory bodies: the institutional review board, the data monitoring committee, the sponsor, and the investigator. This article also reviews and proposes the important steps for compliance and harmonization of globalization of clinical trials.

## 2. Background of Globalization of Clinical Trials

In the process of clinical trials safety and effectiveness of a new drug is tested. When a new drug is discovered and developed by a pharmaceutical company, extensive pre-clinical trials are conducted

prior to testing the drug on people. This pre-clinical process of development of drug ensures the safety of drug for human beings, the starting dose of drug for human clinical trials, and the reaction of new drug on the human body. Once pharmaceutical companies gather enough information regarding the drug these methods can be applied to determine the affectivity of a treatment. As many multinational companies from developed countries have outsourced tasks like computer support and customer service to other countries, pharmaceutical companies have followed the same by outsourcing clinical trials to developing countries like India in addition to the sites in developed countries. India is considered to be a favorable site for conduct of clinical trials as there is large, diverse and untreated population and a pool of patients with both acute and chronic diseases. As the scope of outsourcing clinical trials to developing countries in biomedical research is increasing, ethical and social questions regarding adequate protection of the dignity, rights and welfare of participating human subjects have re-emerged. Recently ethical issues in clinical research are gaining importance because of the concern that research conducted by pharmaceutical companies from developed countries in developing countries like India that is flooded with diseases of almost all types is imposing ethically and morally inappropriate burdens on the host country and the participants in the research trials. This has caused the regulatory authorities to realize the importance of ethical issues to ensure that adequate ethical and economical protection is provided to all persons who participate in international clinical trials.

Since 2002, 15% annual growth has been observed in the number of active Food and Drug Administration (FDA) – regulated investigators based outside the United States, whereas the number of U.S. - based investigators has decreased by 5.5% [12]. This trend suggests that clinical research industry is undergoing the same process of globalization as other industries by outsourcing clinical trials to poor countries [9]. According to Tuff's study in 1997, about 86 percent of F.D.A. - regulated investigators were based in the United States. By 2007, the number of FDA regulated trials conducted in United States decreased to 54%. Pharmaceutical companies from developed countries are looking for developing countries like India because it is often less expensive to conduct clinical trials outside the developed countries and it is easier to find a large group of subjects who had never been treated with medications [9].



**Figure 1:** Clinical Trial Market- Comparative Analysis of Trials among Different Countries  
According to Data in [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

### 3. Reasons for Globalization of Clinical Trials

What are the reasons behind this globalization and dramatic shift in the location of clinical trials? Why India is becoming a preferable site for conduct of clinical trials by pharmaceutical companies from developed countries? There are many underlying reasons responsible for this.

#### 3.1. Access to Subjects

According to a report by Department of Health and Human Services programs sites in India allow pharmaceutical companies from developed countries to recruit subjects quickly and, therefore, bring their drugs to market faster. Subject's recruitment is reported to occur more quickly in India than in developed countries.

#### 3.2. Economical Benefit

Pharmaceutical and biomedical companies gain substantial cost benefits by conducting trials in India.

#### 3.3. Genetically Diverse Population

India is a favorable site for conduction of clinical trials because of its genetically diverse population who have not been exposed to many medications but have pool of diseases, ranging from tropical infections to degenerative disorders.

#### 3.4. Low Infrastructure Cost and Cheap Labor

Almost all Indian doctors speak English, and many have acquired postgraduate qualifications abroad, primarily in developed countries. Besides this cheap labor and low infrastructure costs, which can reduce expenditures for clinical trials by approximately 60 percent, is available in India [18].

#### 3.5. Bureaucratic Regulatory Procedure in Developed Countries

Furthermore, the Drugs Controller General of India (DCGI) — the equivalent of the U.S. Food and Drug Administration (FDA) — is understaffed and lacks the expertise to evaluate protocols. Currently, the technical staff consists of just three pharmacists, including the controller, and just one medically qualified doctor. The reason for conducting clinical trials in developing countries is increasingly bureaucratic and expensive regulatory environment in developed countries. In developed countries the laws and regulations governing the clinical research trials have become more and more complicated which in turn place a greater burden on clinical research investigators for documentation, training and devices on a global scale.

### 4. Regulatory Mechanism for Conduct of Clinical Trials in India

#### 4.1. Regulatory Procedures

The Central Regulatory agency known as the DRUGS CONTROLLER GENERAL (INDIA) or the DCGI is responsible for all procedures related to new drugs including clinical trials in India. All clinical trial applications are submitted to the DCGI office for approval. The documents required as part of the clinical trial application are detailed in Form 44 under Schedule Y of the Drugs and Cosmetic Act. Permission to conduct trials is granted in approximately 3 months from the time of submission. The approval process takes longer if the DCGI's office decides to refer the application for expert feedback to agencies such as the Indian Council of Medical Research (ICMR). If the drug falls under the category of "genetically engineered" or "biologics" then the application is passed through to the

Department of Biotechnology (DBT) and is reviewed by the Genetic Engineering Approval Committee (GEAC). This approval process usually take anywhere between 5 - 6 months. Along with the clinical trial application, an application for import license is made by completing Form 12 of Schedule Y. The application should accurately quantify the drugs imported accompanied with appropriate justifications for the quantities imported. An import license number is issued about 2 weeks after the clinical trial approval is provided. This import license number should appear on all the individual subject drug supplies [2].

If biological samples need to be shipped out of India, an application for export needs to be made to the Director General of Foreign Trade (DGFT).

The Central Drugs Standard Control Organization first issued the Indian Good Clinical Practice (GCP) guidelines in year 2001. These guidelines were subsequently amended and made the law in the year 2005.

Sponsors need to be aware of each of these differences and ensure adherence to Indian guidelines at all times.

#### **4.2. Ethics Committees**

In India most of the hospitals have institutional Ethics Committees for review of clinical trials. These committees are formed as per the guidelines issued by GCP. At a minimum, the documents submitted to committee are Protocol and Investigator Brochure including all amendments, informed consent forms along with translations as well as details of payment or compensation to subjects, if any. Approval is received in maximum of six to eight weeks following submissions. Most Ethics Committees usually charge a fee of approximately 200 US\$ or 170 Euros. Some Ethics Committees chose to provide conditional approval until regulatory approval is received. Once regulatory approval is received, a full approval is provided in a matter of few days [2].

In a reflection of the increasing number of clinical trials being performed in India, several Independent Ethics Committees have begun functioning in the last couple of years. Sponsors usually approach the Independent Ethics Committees when they need to work with potential investigators with a private practice that not attached to a hospital or institution. However, in reality, ethical committees work very differently and rarely follow the GCP guidelines. There is no interest in their impact either. Just a complacent smugness about clinical research opportunities, almost like they are simply commercial ventures on the lines of call centers [2].

The second question relates to social ecology and the genetic makeup of trial populations. Geographically distinct populations can have different genetic profiles, and these differences have been shown to be related to the safety and effectiveness of drugs and even medical devices. Hospital and clinic infrastructure, treatment choices, and quality of care vary widely from country to country. Proper physician training is essential before providing the patients access to medications.

#### **4.3. Informed Consent Process**

Issue of informed consent is very important as far as India is concerned. Illiteracy as well as the possibly blind acceptance of the doctor's advice amongst semi - urban and rural populations naturally rises sponsors' concerns about how truly "informed" the informed consent process is in India. A recent issue of the journal CR Focus published by the Institute of Clinical Research carried an article on this very topic. The authors who are auditors and have audited studies all across the globe concluded that that the informed consent process carried out in India is probably as good or bad as anywhere else in the world [2].

Population of India is large and people speak different languages here. So informed consent document should be translated into the regional languages of the subjects. If the issue is of illiteracy any close relative of the subject can be brought for the process to serve as representative who is legally accepted for the informed consent process and side by side thumbprint impression of the subject can be obtained on the consent form.

As per the Indian guidelines, the subject can refuse to allow his biological material to be stored and used for future evaluations. The Indian GCP guidelines clearly define the content and format of the Informed Consent document and must be adapted for all clinical trials being performed in India.

#### 4.4. Investigators

After USA India has good number of qualified doctors who are GCP trained. Since India is becoming a hub for clinical trials, the number of GCP trained doctors is expected to be doubled in coming two years. Doctors in India possess good communication skills, are well versed in English and are quite familiar with the trends of western medicine practice. According to my opinion sponsors for clinical trials and CROs need to train investigators lacking awareness about GCP guidelines for better results before starting any trial. Investigators participate in clinical trials as they get good opportunities in terms of being associated with international organizations apart from financial reasons. They can also provide free treatment to their patients also and get good grant from sponsors and learn latest techniques of investigation and treatment. All these factors push them towards participation in clinical trials.

#### 5. Ethical and Scientific Considerations of Globalization of Clinical Trials in India

There are obvious reasons for conducting clinical trials in India. But there are certain important ethical and scientific issues raised by globalization of clinical trials [16, 14].

The most important ethical issues raised by the use of human participants in research are beneficence (doing good), non-maleficence (preventing or mitigating harm), fidelity and trust within the fiduciary investigator/participant relationship, personal dignity, and autonomy related to privacy of information and informed, voluntary, competent decision making [1].

In India regulatory body which monitors the quality of clinical trial data and the safety of drugs and devices is the Drugs Controller General of India (DCGI), they have limited information regarding research conducted outside their jurisdictions or countries, including the sites, investigators, and participants and the quality of trial data [12, 10, 17].

Recently practice of unethical and illegal clinical trials has been observed in India which has attracted coverage by media also [11]. Many unethical cases have been observed like in 2002 two new chemicals M4 and G4N were used for the patients suffering from oral cancer at a regional cancer in Kerala which is run by the government. All those trials were done without any regulatory approval [11]. Also in the year 2003 an anticancer drug named Letrozole was used in illiterate women of West Bengal to test for ovulation which was again unethical [11].

Transparency in conducting trials in India is the main concern as far as ethical issues are concerned. The International Committee of Medical Journal Editors has issued guidelines for investigators with regard to participation in study design, access to data, and control over the publication of results [12, 6]. Protection of publication rights for investigators is necessary to the transparency and integrity of research, yet it is an ongoing area of contention for industry sponsors. What should be the criteria for enrolling human subjects in clinical trials? Pharmaceutical industries conducting clinical research



should be responsive to the health needs and priorities of the communities in which the research is conducted.

**Table 1: Issues, Obstacles and Recommendations for Globalization of Clinical Trials in India**

Issue	Obstacles	Recommendations
Transparency of clinical trials in India	Access to clinical data about the trials of the drugs which are not successful is usually not published and publicized	Information about failures of the trials should also be put in a publicly searchable database.
Informed consent	Sometimes surrogate or waved consent is obtained leaving patients unaware that they are in clinical trials particularly in critically ill patients.	An ethically valid informed consent consisting of four key components: disclosure, understanding, voluntaries, and competences should be mandatory before conducting clinical trials on human subjects.  Even if in cases requiring exemption from informed consent like in critically ill patients or if family members are not available community consultation, public notification, and independent data and safety monitoring should be done.
Confidentiality	Sharing information from DNA sequencing, databanks and public health measures is essential for developments of new drugs	Researcher's goals against requiring essential information should be thoroughly balanced against the risk of harm which may occur due to disclosure of important information in an unauthorized way. A strict vigilance is needed in order to win the trust of the public which is an essential element in pursuit of knowledge to win the confidence of the research participants.
Exploitation of research participants	Recent studies have showed that some pharmaceutical companies offer financial inducements to the illiterate blue collared workers more per month to participate in a trial than they ears at their jobs and entice the subjects by providing medications. There is no protocol of continuation to supply the studied medicines free of charge or at affordable charges after completion of trial if found beneficial.	After the trial participants should have access to medicines after the trial if found to be effective they should not only be treated either free of cost or at discounted prices.  A protocol should be made regarding supply of medicines after the trial at affordable charges for the participants.
Regulatory bodies	Regularity bodies like Drugs Controller General of India DGCI are understaffed and lack the expertise to evaluate protocols. Currently the technical staff consists of three pharmacists including the controller and not one medically qualified doctor.	The regulatory bodies should be properly staffed and increase qualified manpower and bringing in more academic expertise to discuss necessary improvement strategies for conduction of clinical trials in India.  The required authority can be delegated to the lower ranks, which would shorten the approval timelines for clinical trials.  The regulatory bodies recognize the need to frame guidelines and regulatory approval processes at par with international standards.

Compensation for participation	Most of the times participants enrolling in clinical trials are not reasonably financially compensated for their participation but simply benefit from free treatment, including doctor consultations, transportation, etc. Participation in clinical trials carries some risk and injury may occur during certain procedures.	<p>Participants should not only receive fair and reasonable monetary compensation for the time and effort they devote for the clinical trials but should also be compensated for any injury if occur during clinical trial.</p> <p>A proper list of approximate monetary compensations for a variety of frequently performed clinical activities should be framed by the regulatory bodies.</p>
Review process	Pharma companies, clinical research organizations and investigators demand immediate reviews from institutional review boards which result in unqualified approval often made without extensive deliberation and scientific insight.	<p>Centralized IRBs should receive more feedback about developments in multisited trials, and a “data safety monitoring board” should review those trials.</p> <p>IRBs should be informed of FDA actions against investigators and notified of prior protocol reviews conducted on the same protocol by other IRBs. They should increase their awareness of research conduct at the sites they review.</p> <p>Educational programs should be instituted for IRB members, along with continuing research ethics programs for participating physicians.</p>
Documentation and communication	Translation of clinical trial documents requires a high level of precision and accuracy compared to other types of documents. Urbanization trends in many developing and emerging countries often result in diverse patient populations with wide and considerable linguistic and cultural differences from area to area and sometimes within a given area in India. Lack of education among research participants in India is thus the biggest challenge.	<p>Documents submitted to the regulatory authorities must be translated into the official language of host country. The documents should be legible, clear, complete, clearly labeled, and accurate and filed in the pre-determined timeframe without any discrepancies.</p> <p>Documentation should be divided into three parts - before list, during list and after list. Before List consists of regulatory and ethics committee approvals, ICFs, subject information sheets, investigator brochures, finance and insurance agreements, investigational product specific guidelines, protocol, randomization lists, and pre-trial monitoring reports.</p> <p>Documentation ‘during’ the trial includes amendments, updates and approvals for them, ICFs and CRFs – completed, signed and dated. Adverse events (AE) reports and notifications, site staff logs, reports of monitoring visits, source documents are also filed.</p> <p>The ‘after’ list reads – audit certificates, final reports to be submitted to the regulatory authorities, trial close out monitoring report, clinical trial materials accountability records, decoding documentation and investigational product destruction records. All these documents are filed in the trial master file and the site master file and they serve to demonstrate compliance with GCP and regulatory norms.</p> <p>Documentation should comply with the necessary regulations and guidelines and their location and date of filing must be easily identifiable. Good documentation should ensure to fully reconstruct the trial even after it has been completed.</p>



Post trial access	There is no regulatory requirement for provision of medications after completion of trial. Sometimes medicines are not available at all or are too expensive for the patients to afford.	As per WMA declaration of Helinskiy, it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review  Patients who take on the inconvenience and potential risks of a medical research study should have access to the best proven prophylactic, diagnostic and therapeutic methods that result from the study.
Professional competence	In many cases the investigators involved in clinical trials are not sufficiently well trained to cope with advanced multidisciplinary environment. Training lacks minimum set of common requirements which undermines the scientific validity of trials.	Investigators involved in clinical trials should be thoroughly trained to cope with recent advances.  This includes skill in counseling, informing and communicating adequately, participating in the decision-making process with respect to clinical trials.
Communication	There is no direct communication between industry and DCGI's office. So some applications are queried outright without checking the information.	An environment for effective interaction between regulators, industry and academia should be created. Regular meetings should be organized to discuss different issues.

## 6. Discussion and Conclusion

Although globalization of clinical trials has received considerable attention but there are certain ethical and scientific concerns that need to be taken care of as little attention has been devoted in quantifying the dimensions of such controversies. In this paper we have tried to bring such issues to the surface reflecting why India is considered to be a favorable destination for pharmaceutical companies for conducting clinical trials. There are two types of factors influencing participation of human subjects in clinical trials in India- one is the factors favoring participation and other is the factors restricting the participation. Factors favoring participation includes extra source of income, personal health benefits and motivation to participation in research for welfare of humanity.

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. Given the influence of an incentive, its ability to distort potential participants' judgment towards trial participation is significant [16]. Rapid enrolment of participants in clinical trials, huge and racially diverse population ensuring generalizability of results also makes India an attractive destination for clinical trials.

Clinical testing in developing countries like India is also attractive to pharmaceutical and device companies because it can help them overcome regulatory barriers for drug approval in these countries in which the population size alone offers the promise of expanding markets [13].

Factors restricting participation include loss of confidentiality, concern about safety of drugs in trials and mistrust on pharmaceutical industries conducting trials.

Recent studies have showed that some pharmaceutical companies offer financial inducements to the illiterate blue collared workers more per month to participate in a trial than they earn at their jobs and entice the subjects by providing medications. There is no protocol of continuation to supply the studied medicines free of charge or at affordable charges after completion of trial if found beneficial.

Sometimes participants enrolling in clinical trials are not reasonably financially compensated for their participation but simply benefit from free treatment, including doctors' consultations, transportation, etc. Participation in clinical trials carries some risk and injury may occur during certain procedures.

In our opinion various prerequisites should be considered so as to have a positive effect of globalization on health of participants in clinical trials and to address ethical concerns raised by globalization of health (Table-1).

A careful effort to streamline regulations governing clinical trials could reduce redundancy in the system while ensuring ethical conduct. Improved research efficiency would decrease the differential costs of research among countries and increase the likelihood that trials are initiated in the countries where the drugs being tested will be sold. Greater use of centralized institutional review boards, standard terms for research contracts, and the development of streamlined best practices to reduce unnecessary work for investigators and medical institutions are needed [5, 4].

It is the complete responsibility of the research organizations and pharmaceutical industry sponsors that all the trials should meet ethical guidelines so as to face the challenges posed by globalization [12].

Documentation should comply with the necessary regulations and guidelines and their location and date of filing must be easily identifiable. Good documentation should ensure to fully reconstruct the trial even after it has been completed.

Participants should not only receive fair and reasonable monetary compensation for the time and effort they devote for the clinical trials but should also be compensated for any injury if occur during clinical trial.

A proper list of approximate monetary compensations for a variety of frequently performed clinical activities should be framed by the regulatory bodies.

Investigators and sponsors involved in clinical trials should make best possible efforts to maintain confidentiality and access to medicines that have been proven effective for the participants.

Research proposals for clinical trial conduction submitted to ethics review committees should underline how new interventions that if proved to be effective from the research will become available in host country after the completion of trial. Pre-research negotiations among sponsors, host country officials, and other appropriate parties should be described thoroughly how such interventions will be made available.

Clinical trial participants take risks and accept inconveniences to promote the advancement of medicine. Hence to avoid exploitation and to maintain a good relationship between the investigators and participants, they deserve benefits in return for their contribution. Therefore, providing them successfully tested drugs is a good way of avoiding exploitation. NBAC also concludes that at the end of a clinical trial that results in an effective intervention, research participants should be provided with this intervention. In addition, NBAC also maintains that before initiating a research project, researchers or sponsors should consider how they might make benefits, if any, available to others in

the host country, with the understanding that appropriate host country decision makers must be meaningful and essential participants in making such arrangements.

Thorough review and proper assessment of different regulations governing clinical trials in India is required so as to get international acclaim in the field of clinical trials [19]. All the regulating factors need to be streamlined. Government should increase spending on clinical trials so that ethical issues can be dealt easily. Proper training should be given to the investigators in India regarding ethical and scientific considerations as well as design and process of clinical trials.

Transparency of clinical trials is the most important issue in India. Information about failures of the trials should also be put in a publicly searchable database.

Accordingly, provisions for the publication of all clinical trial data and protection of publication rights for investigators should be preserved, independent of sponsorship [12]. We suggest that to ensure the ethical and scientific integrity of clinical research globally and to promote harmonization of international research it is first necessary to overcome the barriers and provide thorough and complete information about the benefits and risks of new drugs in a publicly searchable database.

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