THE ROLE OF INSTITUTIONAL ETHICS COMMITTEES IN CLINICAL TRIALS: A STUDY OF SELECTED HOSPITALS IN NEW DELHI

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ROHINI KANDHARI

CENTRE OF SOCIAL MEDICINE AND COMMUNITY HEALTH
SCHOOL OF SOCIAL SCIENCES
JAWAHARLAL NEHRU UNIVERSITY
NEW DELHI- 110067
INDIA
2011

CENTRE OF SOCIAL MEDICINE & COMMUNITY HEALTH
SCHOOL OF SOCIAL SCIENCES
JAWAHARLAL NEHRU UNIVERSITY
NEW DELHI - 110 067

Certificate

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This is to certify that the dissertation entitled '**The Role of Institutional Ethics Committees in Clinical Trials: A Study of Selected Hospitals in New Delhi**' is submitted in partial fulfilment for the award of the degree of Master of Philosophy (M.Phil) of the University. This dissertation has not been submitted for the award of any other degree of this University or any other University and is my original work.

Rohini Kandhari
Rohini Kandhari

We recommend that this dissertation be placed before the examiner for evaluation.

Mohan Rao
Prof. Mohan Rao
Supervisor

Rama Baru
Rama Baru
Chairperson
Chairperson
Centre of Social Medicine & Community Health, SSS
Jawaharlal Nehru University
New Delhi-110067

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Contents

Abbreviations

CIOMS	Council of International Organizations of Medical Sciences
CRO	Contract Research Organization
CTRI	Clinical Trial Registry of India
DCGI	Drugs Controller General of India
FDA	Food and Drug Administration
FICCI	Federation of Indian Chambers of Commerce and Industry
GATT	General Agreement on Tariffs and Trade
GCP	Good Clinical Practice
HHS	United States Department of Health and Human Services
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICMR	Indian Council of Medical Research
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
NME	New Molecular Entities
OHRP	Office for Human Research Protections
PI	Primary Investigator
RCT	Randomized Clinical Trial
TRIPS	Trade Related Intellectual Property Rights
WHO	World Health Organization
WTO	World Trade Organization

Introduction

"In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests" (World Medical Association, Declaration of Helsinki, Guideline 6, 2008:1). The guardian of this fundamental ethical code of clinical research is the institutional ethics committee. Institutional Ethics Committees (IEC), also known as Institutional Review Boards or Ethics Review Boards, are independent bodies comprising members from medical and non-medical backgrounds who are responsible for ensuring the safety, integrity and human rights of research subjects participating in a clinical trial (World Health Organization 1995).

Across the world, any agency conducting biomedical research on human subjects must seek approval for their research proposal or trial protocol from an ethics committee before the clinical trial begins. A clinical trial[1] uses human research subjects to determine if biomedical interventions such as drugs, treatments, devices or new ways of using known drugs, treatments or devices are safe, efficacious and effective. Risks are inherent to a clinical trial as research subjects are exposed to interventions or treatments whose safety and effectiveness on human beings is still unproven until Phase III or the last confirmatory phase of drug development is successful. The idea of instituting the requirement of ethical review of a clinical trial protocol in national policy gathered momentum in the West, in the 1960s and 1970s, particularly in the United States (U.S.). This was a time when ordinary people had begun to question established ideas and beliefs about authoritarian and discriminatory social, economic and political structures. Unethical experiments performed on vulnerable populations such as prisoners, racial minorities and the mentally challenged had become public knowledge and people needed assurance from the state that the scientific community would protect the rights and welfare of the research subject. Many ethically questionable medical experiments conducted during the Second World War, as well as later in the 1950s and 1960s, were being justified by their perpetrators. These experiments reflected a tussle between scientific progress on the one hand and the interests and rights of an individual on the other. When the

[1] A clinical trial is also used to test behavioural interventions such as diet, cognitive therapy or a physical activity. This document refers only to clinical trials that are conducted to test drugs, treatments and medical devices.

pharmaceutical industry moved its clinical trial operations to the developing world, different ethical concerns emerged. In the new kind of global clinical trial, commercial interests that frequently conflicted with the rights of the research subject replaced the values of advancing scientific knowledge in order to reduce the burden of disease. While the utility of the clinical trial both as the only method that can prove the safety and efficacy of a treatment and as a potential tool for serving public good is indisputable, the uncomfortable question that emerges from the long history of unethical experimentation in clinical trials is - "but a good to whom and an evil to whom?" (Jonas 1969: 226).

In 2005, the Government of India (GoI) amended its drug development laws to allow the global pharmaceutical industry to conduct clinical trials in India concurrently with other trials being run outside the country. Before the amendment, clinical trials for new drugs of foreign origin were permitted only if the later phase had already been undertaken outside India. For example, Phase II trials could only be conducted in India if Phase III trials had taken place elsewhere and Phase III trials were permitted only if the drug had been approved for marketing in a foreign country. These regulations were important safeguards that protected Indians from being treated as first line research subjects. After 2005, Schedule Y of India's Drugs and Cosmetics Rules—hereafter referred to as the Rules—was revised and the protective 'phase-lag' crucial for the safety of clinical trial subjects or research subjects was removed. This revision to the Drugs and Cosmetics Act meant that now Phase II and III trials of new drugs of foreign origin—those that have not yet been approved—could be conducted in India, while they were simultaneously also being tested elsewhere.

Although the numbers of clinical trials being conducted in India are relatively few compared to the West, the number of industry-sponsored clinical trials in India has increased significantly after liberalization of its drug development policy. Simultaneous with this increase in the number of trials being conducted are accounts of illegal and unethical clinical trials that compromise the health and safety of hundreds of research subjects. In 2010 alone 671 deaths were reported to have occurred in clinical trials in India (Mathew 2011). In the context of the industry-sponsored clinical trial and increasing accounts of ethical violations, this research

study attempts to critically examine the role and function of Institutional Ethics Committees in selected hospitals in Delhi and the challenges faced by their members.

The review of literature emphasises the importance of an ethics committee by describing its origins in the murky world of medical experimentation on populations in the West and the movement of unethical clinical research to developing countries like India. The chapter also reviews various ethical guidelines that developed specifically for the protection of human subjects in clinical research, the recognition of ethics committees in these guidelines and the debates around the ethics of conducting clinical trials in the developing world. The review of literature is followed by a discussion on the multinational drug industry that is the major sponsor of clinical trials today. While the drug company does not conduct a clinical trial with intent to harm research subjects, its commercial interests often takes precedence. Ethical norms are overlooked and violations that become public knowledge are suppressed by the industry in its eagerness to get a drug or vaccine on the market. An IEC is responsible for ensuring that the ethical principles of Justice, Autonomy and Beneficence govern the process of every clinical trial. A trial can be just only if the risks and benefits of research are distributed equally among sections of the population, but the ground realities of conducting research in the developing world suggest otherwise. Research subjects could represent socially and economically disadvantaged sections of the population. Large numbers of research subjects are integral for the industry in the later phases of clinical trials in order to obtain favourable and statistically significant outcomes of the intervention being tested. The sections of the population in both the developed and developing world that would offer themselves as research subjects are impoverished groups who cannot afford basic health care. Only in the developing world can such large numbers of willing subjects be procured. Obtaining consent to participate in a trial is easier in India because free treatment and payment for participation are greater incentives for the poor. The drugs tested on them are not usually breakthrough treatments and most likely the drugs will not be available and affordable to the research subjects after the trial is over. Chapter one discusses the nature of drug development today that has given rise to a global enterprise that appears to be driven by commerce and patent monopoly with little regard for the safety of research subjects or health priorities of host nations. It provides the context in which ethics committees operate, the role of the different actors involved in the

clinical trial, the reasons why India has the potential to become an attractive destination for clinical trials and why Indians are vulnerable to the clinical trial industry.

Ethical violations in clinical trials conducted in India are evidence of the neglect of IECs and their failure to protect the rights and welfare of the research subject. There is little information about the functioning, structure and composition of these committees. Studies on ethics committees are confined to a few surveys and there are no experiential accounts of ethics committee members. The critique of IEC functioning and performance is the same the world over. Their understanding of ethics is typically restricted to ensuring that investigators and sponsors have completed all the necessary paperwork and that informed consent documents contain appropriate information about the clinical trial. In addition, members of IECs are far removed from the unequal context in which clinical trials are conducted. They have no interaction with research subjects even though they are the only agency entrusted with the primary duty of protecting them. Critics argue that ethics committees are redundant bodies because their members cannot override the interests of the institution—with which they themselves are associated—that needs the industry-sponsored clinical trial as a source of revenue. They call for greater stringency in ethical oversight and the need for an unbiased and independent ethical review. Others argue that stricter rules and regulations will still not change the unequal context in which clinical trials are conducted in India. Chapter three describes some of the essential tasks of an ethics committee prescribed by international and national guidelines and regulations for the protection of human subjects in biomedical research. The chapter also analyses the problems in the implementation of these tasks and limitations of ethical guidelines and principles in providing constructive assistance to IEC members so that they can do their job effectively. Chapter four analyses the findings of the research study that has attempted to fill the gaps in the knowledge of ethics committees and, more importantly, describes the challenges and constraints faced by ethics committee members.

Four essential arguments are made across different chapters. Firstly, the role of the IEC in the context of the current business model of clinical research and the structural inequalities that are inherent to a clinical trial cannot be overemphasized. Secondly,

the enormity of an ethics committee's responsibilities needs to be understood in the context of ethical dilemmas and challenges of clinical research in the developing world that remain unresolved. Thirdly, knowledge of the problems and constraints faced by each IEC member is essential if ethical oversight has to be improved. Fourthly, reasons for ethics committees not performing their duties effectively, efficiently and responsibly are compounded by limited guidance available to ethics committee members on how to navigate their complicated tasks and bring the ethical principles of justice, autonomy and benefit to the clinical trial process.

Chapter One

The Globalized Clinical Trial: Establishing a Context for the Institutional Ethics Committee

Introduction

In order to understand the significance of an IEC in regulating the ethical conduct of clinical research in India, it is important to examine the global context in which the regulatory body operates. The most influential stakeholder in the clinical trial industry is the multinational drug company. With assistance from the contract research industry and with support from the state and the academic community, the pharmaceutical industry has positioned its research agendas and interests at the forefront of the global clinical trial.

Multinational drug companies and biotechnology firms are the main sponsors of clinical trials across the world. More than half the clinical research projects in the U.S. are sponsored by the pharmaceutical industry (Petryna 2009). In India too, data analyzed from the clinical trial registry of the year 2009 indicates the pharmaceutical industry's significant presence in clinical trial sponsorship. Prior to 2006 there were 29 pharmaceutical sponsors of clinical trials in India compared to 350 in the year 2009 (Ravindran and Nikarge 2010). Over 60 percent of the global pharmaceutical market share belongs to the pharmaceutical industry operating in the U.S. (Petryna 2009: 208). The industry today is a global business with several European companies having shifted their Research and Development operations to the U.S. for reasons that include the country's unregulated drug price system that facilitates greater profitable business options and the exceptional research output of American universities (Angell 2004). It has among the most powerful political lobbies in the capital, Washington D.C., and has been highly influential in the formation of national and global policies—such as the Trade Related Intellectual Property Rights (TRIPS) agreement—that cater to industry needs. The industry's influence has permeated global research agendas, the kinds of drugs being tested in clinical trials, the kind of research being published and the kinds of drugs being prescribed by the medical profession (Angell 2004; Petryna 2009). With its powerful lobbying on global trade and economic policy, the drug industry has managed a twenty-year patent protection regime on its intellectual property. While it has suffered in recent years from the lack

of true innovative therapies it has still managed to amass relatively higher profits than any other industry primarily by developing drugs similar to existing lucrative ones and by aggressive branding and marketing it captures already successful markets. From the 1980s onwards the pharmaceutical industry has been the most profitable industry in the U.S. and the clinical trial industry has become one of the most profitable sectors for drug companies (Angell 2004; Petryna 2009). For example, in 1990, the ten leading pharmaceutical companies (that also included European firms) had profits of nearly 25 percent of their sales (Angell 2004:10).

Critics of the industry like Marcia Angell, former editor-in-chief of the *New England Journal of Medicine*, argue that in recent decades, the pharmaceutical industry has "moved very far from its original high purpose of discovering and producing useful new drugs. Now primarily a marketing machine to sell drugs of dubious benefit, this industry uses its wealth and power to co-opt every institution that might stand it its way..." (Angell 2004: xxv-xxvi). Academic institutions in the U.S. conduct the initial stages of drug discovery and then license their discovery to the richer drug company or biotechnology firm for development. Drug development is an expensive and risky business—with vast amounts of money invested in a drug that may not make it to the market and patents have to be filed before clinical trials begin in order to prevent imitation from a competitor. The stakes of the clinical trial industry are therefore high.

Drug companies need larger numbers of research subjects to have enough evidence to indicate that their drug is better than an existing one. They also need 'treatment naïve' populations or those who are not undergoing any treatment for a condition or disease, as drugs in the body at the time of a clinical trial can interfere with the trial's outcomes (Petryna 2005). In search for large numbers of research subjects that are hard to find—and sustain throughout a trial—in the developed world, the global clinical trial has come to India where treatment naïve individuals and also patients are easier to recruit because basic health care is inaccessible, unaffordable and unavailable to most. Physician-investigators in India are eager to promote their individual career prospects and institutions need an additional source of revenue to improve working conditions and upgrade their infrastructure. The clinical trial brings hope for improved health and is also a potential source of income for both the impoverished patient and the resource-starved institution. The multinational drug

industry is interested in marketing the drug or treatment as soon as possible and the Contract Research Organization's (CRO) interest lies in bringing in as much as business as possible from the industry. The CRO has to therefore ensure the creation of a regulatory framework that conforms to international standards and must assist the sponsor in the necessary paper work to get the trial started. Responsibility to the research subject and to larger public health benefits of clinical research can often be lost in the individual interests of these different groups. Examples of disregard for research subject safety by the multinational drug industry are discussed in greater detail in chapter two.

This chapter attempts to explain the role of the different actors in a clinical trial process. It provides a background to some of the essential features of the global pharmaceutical industry, its rise to power, and the expansion of its clinical trial operations to countries like India that offer easier and quicker recruitment of trial subjects, cheaper infrastructure to conduct clinical trials, willing physician-investigators and a friendly regulatory environment.

I. The Global Pharmaceutical Industry: A Background

1. The development of Big Pharma: the university, industry and biotechnology nexus

The 1980s were a watershed time for the rise of the globally influential pharmaceutical industry (Angell 2004) and by the turn of the century it was the most profitable industry in the U.S. economy (Tyfield 2010). The rise of Big Pharma—a term that denotes the largest, transnational pharmaceutical companies in the U.S. and Europe (Angell 2004; Tyfield 2010)—must be understood in the context of neoliberal reform in America's domestic policy in the 1980s, and of the rise of neoliberal hegemony in the global South. The dominance of neoliberal polices in the 1980s was marked by a regrouping and restructuring of economic and political interests in the U.S. and abroad that proposed a shift to financialization of the economy and restoration of power to the business elite (Harvey 2005). The economic recession of the 1970s replaced Keynesian policies of strong state intervention and welfare safety nets for the public with the neoliberal doctrine that prescribed living in a society characterized by free trade, free mobility of capital, free markets, private appropriation of public resources and the rights to private property including that of

the production of knowledge. The U.S. in the early 1970s witnessed large-scale mobilization of national business organizations and think tanks to aggressively promote neoliberal values among universities, business schools, and the media. (Harvey 2005).

Big pharma like other industries were also affected by the economic crisis of the 1970s. Research and development costs were high and the industry was facing competition from generic drug or off patent drug manufacturers from the developing world. The global pharmaceutical industry's attempt to suppress the threat from cheaper, off patent drugs and make it harder for generic drug manufactures to copy patent drugs culminated in the TRIPS agreement that will be discussed in the following pages. Moreover, this was a time when federal regulatory requirements were getting more stringent after the Thalidomide drug scandal of the 1960s. Thalidomide that was promoted for its use on pregnant women—without adequate testing on animals and on humans—resulted in several thousand abnormal births among infants of women who had used the drug. Henceforth, drug safety regulations in the U.S. became tighter with drug companies having to also prove drug efficacy using the randomized and double-blinded controlled trial (Petryna 2009). The controlled and Randomized Clinical Trial (RCT) came to be considered as the gold standard of clinical research. In a RCT, one group of research subjects is given the treatment or drug under investigation and another group of research subjects is given another treatment or drug or not given any treatment at all, also known as placebo. The trial is therefore described as a controlled trial. The term 'randomized' implies that research subjects are ascribed to different groups by chance. This method is used to reduce bias among investigators who can otherwise assign research subjects who they predict will have the most favourable outcomes to the treatment that the investigator considers to be better than the one used for the comparator group. The term 'double-blind' implies a situation where neither the investigator nor the research subject is aware of who is in the control or treatment arm of the trial. This method is also used to prevent any bias on the part of the investigator and the research subject (Levine 1988).

The expense of drug development compounded by an increasing complexity in the methods of drug development brought the pharmaceutical industry together with two

other sectors: life science departments of universities and the emerging biotechnology business.

The collaboration of the pharmaceutical industry with universities and biotechnology firms gave further impetus to the growing political and economic clout of drug companies. American universities that had enjoyed an increase in federal funding for scientific research after the Second World War (World War II) and had operated relatively independently of the drug industry so far were faced with a budget crunch in the 1970s and 1980s due to cuts in federal sponsorship of research. The academic institutions in need of funds turned to corporate support. Universities, at this time, were criticized for excessive spending of public funds on irrelevant research, but were also regarded as potential sites for exploiting new ideas and discoveries by turning them into profitable consumer products. The university and the industry had to come closer together in order to market potentially profitable discoveries (Krimsky 2003). With President Ronald Reagan's pro business, neo liberal administration, several changes in economic policy were instituted in the 1980s that favoured university-industry collaboration.

The Bayh-Dole Act enacted in 1980 was one such policy that was largely responsible for the growth of the pharmaceutical industry and its inroad into academic controlled research (Angell 2004). It allowed universities, non-profit institutions and small business to patent their discoveries or intellectual property facilitated by government supported research, and then grant licensing rights to companies that can market the drug and also pay royalties to the university (Angell 2004). Before the legislation, a public funded discovery was available to any company to use. Since the passing of the Bayh-Dole Act, the number of patents granted to universities has risen from less than 300 a year to more than 3000. Prior to the Bayh-Dole Act financial benefits to a university from licensing was negligible but now a U.S. university can earn two billion dollars in a year (Sampat 2010: 755).

2. The patent regime and its impact on the clinical trial process

A patent is granted to a product or a process when there is usefulness; novelty or difference from earlier inventions and is not obvious to a person who is knowledgeable in the particular field. It can apply to either the drug substance or chemical composition; or the use of the drug for a particular condition; or the drug

formulation or the process of manufacture (Angell 2004; George 2007). Patents are important to the pharmaceutical industry because once a patent is granted it provides monopoly rights to the particular drug company to make that drug and no other company can market that drug for the patent period. An application for a patent is usually filed before the clinical testing stage begins to protect the confidentiality of drug information and to prevent competition from other companies during the clinical trial period (Angell 2004). Once the drug comes off the patent period, however, then generic versions are allowed to come into the market and prices of the brand-name drug can fall drastically. Therefore it is important for big pharma to extend patent rights and keep generic drugs off the market, as extending the years of a patent can potentially add billions of dollars to drug sales (Angell 2004) especially for blockbuster drugs—that have sales of more than a billion dollars a year—such as Prozac, Lipitor and Viagra (Petryna 2009).

Patent protection—which means that no other company can sell or market the product for a fixed period of time—was also important for the newly developing biotechnology firms. For the biotechnology business Research and Development (R&D) expenses are usually as high as fifty percent of sales (Dutfield 2003: 153 cited in Tyfield 2010: 69) and therefore the business needs protection from the potential leakage of trade secrets. In the 1970s, biotechnology led to several breakthrough discoveries in recombinant DNA techniques. These new technologies in genetic manipulation that were initially developed without the intention of commercial exploitation, later presented to the neoliberals new opportunities for investment and therefore another means of expanding capital (Tyfield 2010).

Other laws were passed in the U.S., in the 1980s and 1990s, to increase the patent life of brand name drugs, resulting in an increase in monopoly rights of such drugs from eight years in 1980 to fourteen years by the year 2000 (Angell 2004: 10). Since many academic researchers and their affiliated institutions owned equity in the newly formed biotechnology companies, the patent licensed to a drug firm by a university or a biotech company, benefited all parties concerned. The collaboration between academia, industry and biotechnology, thus, proved to be a highly lucrative one.

- **The Trade Related Intellectual Property Rights (TRIPS) agreement and data exclusivity**

The Trade Related Intellectual Property Rights or the TRIPS agreement of the World Trade Organization (WTO) followed the post Second World War General Agreement on Tariffs and Trade (GATT). The TRIPS agreement that was initiated on January 1 1995 is "one of the most important neoliberal developments in global economic regulation...representing the construction of public international law by, and in the exclusive interests of, a tiny handful of transnational corporations..."(Tyfield 2010:60). Maneuvered by the multinational pharmaceutical industry, TRIPS instigated a product patent regime in order bring about a global harmonization in minimum standards and consolidation of intellectual property rights.

Among the key changes in intellectual property law that TRIPS instituted was the enforcement of patentability to all "commercially exploitable products and process" (Tyfield 2010: 64) for a minimum period of twenty years. This agreement had serious implications for developing countries like India, who prior to TRIPS did not recognize patents on medicines and food products. Although TRIPS member countries are free to decide which patents to grant, the agreement faced great opposition particularly from countries like Brazil and India (Tyfield 2010). In India, patent laws did not recognize product patents allowing for a thriving domestic generic drug industry that produced off patent, affordable medicines by reverse engineering or making cheaper drugs that have the same active ingredients as the costly patented drugs. By signing TRIPS, the process of reverse engineering would not be possible and India's access to affordable essential medicines would be undermined. In spite of the stiff resistance to TRIPS, the developing world had to eventually make their domestic laws TRIPS-compliant, each country, being given different time lines to concede to TRIPS.

It was at the 1994 Uruguay round of the General Agreement on Tariffs and Trade (GATT), when India committed to becoming TRIPS-compliant by the year 2005. Prior to the deadline it had to provide a mailbox for the filing of patent applications from the year 1995 and provide exclusive marketing rights to products that were given patent protection elsewhere. Signing TRIPS for India meant that the country had to amend its 1970 patent act that had only permitted patents on processes and not

on products. The 1970 Indian Patent Act that had abolished the colonial law that recognized product patents had also reduced the period of protection from sixteen years to seven years. India's 1970 patent law, together with other restrictions on the amount of foreign equity in Indian drug companies, facilitated the growth of a self reliant, pharmaceutical industry that became known for its production of affordable medicines made possible by the reverse engineering of costly patented drugs. Generic equivalents of drugs are much cheaper than patent drugs sold by multinationals and therefore more affordable to the developing world (Gulhati 2010). Due to the product patent regime initiated by TRIPS India's pharmaceutical industry will now have to pay royalties or a license fee to patent holders, resulting in an increase in drug prices.

Although proponents of TRIPS claim that a strong patent regime would foster innovation in India's domestic pharmaceutical companies and upgrade its pharmaceutical industry via Foreign Direct Investment, critics argue that TRIPS has shifted the balance of power to the developed world (Tyfield 2010) and has undoubtedly undermined India's position of being among the world largest producers of low cost drugs and also as exporters of cheap life saving drugs like anti-retrovirals for HIV/AIDS patients (George 2007).

The only allowances given to member countries under TRIPS—reaffirmed during the 2001 Doha Declaration of WTO—is the freedom to decide the method of implementing the agreement within the framework of the country's own legal system and the provision of certain flexibilities such as the option of issuing a compulsory license to a non-patent holder to manufacture a patented product for local use without permission from the patent owner (*The Lawyers Collective* 2007).

Negotiations by the developed world to strengthen intellectual property law did not end with the signing of TRIPS. While strong opposition from developing countries prevented an attempt to remove flexibilities within the Agreement, attempts to coerce developing countries to further strengthen their intellectual property provisions to go beyond the twenty-year patent monopoly imposed by TRIPS—known as TRIPS-plus—continue. TRIPS-plus is being pursued through the World Intellectual Property Organization and bilateral Free Trade Agreement negotiations initiated by the U.S. or the European Union with developing countries and not the WTO. Among the TRIP-plus provisions that the pharmaceutical lobby is attempting to impose and one that has

serious implications for India is the provision of data exclusivity for a specified period (Medicine Sans Frontieres 2009; Nagarajan 2010).

Data exclusivity refers to the exclusive rights given to drug companies to keep their clinical trial data about the safety and efficacy of a drug—which is submitted to the drug regulatory authority to acquire permission to market the product—confidential for a period of five to ten years. Currently, the drug regulatory authority of India, for example, has access to a company's clinical trial data that it can use to verify the safety and efficacy of generic drugs. The generic drug manufacturer who currently has access to a drug company's clinical data only needs to provide the licensing body with the information that the generic drug is equivalent to the brand name drug. Generic drug companies are not required to conduct clinical trials to prove efficacy and safety of drugs as clinical testing on human subjects has already been done by the companies of brand-name drugs. If the data exclusivity is implemented, the generic industry will have to either wait until the exclusivity period is over or produce its own data by going through the elaborate and expensive process of repeating clinical trials. Repeating clinical trials for marketing generic drugs has serious ethical implications for those trial subjects who would be placed in a control group of a clinical trial. In a control group trial subjects can be given no treatment so that they can be compared with another group who is given the drug being tested. The subjects in a control group would therefore be denied treatments for which there is data already available to prove the safety and efficacy of the drug. Data exclusivity also applies to those drugs that are off patent, but the exclusivity provided will act like a patent, essentially preventing all competition and allowing a pharmaceutical company to increase prices on even off patent drugs. (Angell 2004; Hiddleston 2006; Medicine Sans Frontieres 2009).

The neoliberal development of the control of intellectual property instituted in the World Trade Organization's TRIPS agreements represented the specific interests and international influence of the pharmaceutical industry of the developed world and signified "key neoliberal designs regarding both globalization and the construction of a knowledge-based economy..." (Tyfield 2010: 60). The rules under TRIPS also provided an ideology to bring about a consensus among different interest groups—big pharma, the biotechnology business and the university. The coalition that had grown

in political influence due to domestic patent reforms in the early 1980s now favoured changes in global patent policies (Tyfield 2010). The TRIPS agreement essentially gave the pharmaceutical industry what it wanted: that is, the tightening of patenting in the life sciences.

3. Time is precious in the patent regime: the entry of the CRO

Since clinical trials eat into the patent time of the drug being tested, drug companies are in a hurry to complete their clinical trials and market the drug. As the pharmaceutical industry became more powerful and more profit driven it wanted quick results and was not willing to wait for academic researchers to produce theirs. The industry turned to the new profit driven, time-efficient, and resourceful Contract or Clinical Research Organizations for its clinical research needs. In 1990, about eighty percent of industry-sponsored trials were done at academic institutions but within a decade the share dropped to less than forty percent (Angell 2004:101). In 2001, there were about one thousand CROs operating world over with revenues from their drug company clients, amounting to about seven billion dollars (Angell 2004). The CROs who have a network of private doctors and who conduct clinical trials, offer services to trial sponsors that include fulfilling regulatory requirements and procedures, the clinical trial design, medical writing for a clinical trial application, clinical trial data management and clinical trial site management. Contract Research Organizations also claim quicker subject recruitment than academic institutions (Petryna 2009; Drabu, Gupta and Bhadauria 2010).

About one-third of drugs marketed by major drug companies today, are a result of public funded research licensed from universities or biotech companies and these are more likely to be an outcome of innovative research (Angell 2004: 23). The university researcher however, is no longer independent of the industry and has had to become increasingly accommodating to drug companies in order to compete with the growing contract research industry. University researchers have, however, not lost out entirely in the new scenario of the clinical trial industry. In addition to holding equity in drug companies, several academic scientists also undertake profitable consultancies with drug companies, serve on company boards and are speakers at symposiums sponsored by the drug industry. In the year 2001, five doctors admitted to accepting kickbacks

from Takeda Abbot Pharmaceuticals for writing prescriptions for the drug Lupron used in prostrate cancer treatment (Nagarajan 2011).

4. Research and Development (R&D)

In essence, the pharmaceutical companies of the U.S. and Europe rely on academic research—supported largely by the U.S. National Institutes of Health and biotech companies—for the early, but crucial stage of clinical research. The drug industry with assistance from the CRO comes in at the clinical phase of drug development that involves clinical trials using human beings as research subjects.

The early stages of drug discovery are crucial to the process of drug development. In order to develop a drug that will potentially be safe and effective in treating the particular disease being investigated it is necessary to first understand the underlying cause of the disease. The knowledge of the disease at this stage is at the basic molecular level—for example, understanding the processes by which genes are altered or how protein interacts in cells—and it is only with this basic understanding of the disease or condition and the processes by which it affects a human being can the process of developing a drug begin. After acquiring a basic understanding of the disease, the researcher has to then identify the single molecule—a gene or protein associated with the disease—for the drug to target. This target molecule will then be tested using living cells and animals to verify its association with the disease. Following the identification of a target that could potentially be affected by a drug, researchers begin to identify and develop drug candidates or lead compounds that have the potential to become the drug. These lead compounds will then be screened further in animals and cell cultures for an early evaluation of their safety. From this initial screening, the drug candidates will be prioritized. These drug compounds can also be structurally modified to enhance their potential as the ones most likely to be successful (Angell 2004: 23; Pharmaceutical Research and Manufacturers of America 2007).

The preclinical testing stage is essential to investigate the workings of the drug candidate and its safety before human subjects can be exposed to it. However, the pharmaceutical industry claims that only one in one thousand drug candidates pass the preclinical testing stage and of this number, only one in five drug candidates reach the clinical phase of drug development. The total time taken to develop a drug from the

early stages of the preclinical phase until a drug can be marketed ranges anywhere between six to ten years. "Paradoxically, although it is the least creative part of the process, clinical testing is the most expensive" (Angell 2004: 23). The clinical stage comprises four phases:

Phase I

In Phase I of the clinical trial process the drug is tested on human beings for the first time usually on a small number—twenty to eighty—of healthy volunteers. Phase I studies are conducted with the primary objective of investigating whether the drug is safe for humans and at what level of toxicity. The Phase I trial is used therefore to determine: the drugs pharmacokinetic information or how the drug is absorbed by the body, distributed, metabolized and excreted by the body; the pharmacodynamics of the drug or the desired side effects or adverse reactions to the drug (Levine 1988; Indian Council of Medical Research (ICMR) 2006; Petryna 2009) and the safe dose range of the drug. Phase I trials can also be used to obtain early evidence of a drug's effectiveness, however, this early assessment of drug activity is the secondary objective of the Phase I clinical trial.

Phase II

If it has been established in the first phase that the drug tested can be developed further, a Phase II trial is conducted on a few hundred patients who have the condition or disease under study. A Phase II trial is conducted with the primary objective of evaluating the drug's efficacy, its effective dosage range and to further investigate the drug's safety in human beings. The Phase II trial is a closely monitored, controlled trial in which the drug is administered in different doses to one group of patients and the effects are compared with another group pf patients who have not been given the drug (Levine 1988; Angell 2004).

Phase I and II

For research on diseases such as HIV/AIDS and cancer, Phase I and II trials are combined and patients suffering from the relevant disease instead of healthy volunteers are selected for the trials. This is because the toxicity of anti-retroviral drugs or anti-cancer drugs would expose healthy volunteers to unnecessary risks that would outweigh the benefits of the research (ICMR 2006).

Phase III

The Phase III trial is conducted to confirm the safety and efficacy information of the drug acquired from earlier phases and to obtain additional information of effectiveness for specific indications (Levine 1988) in larger numbers—hundreds to several thousand—of patients (Angel 2004). The Phase III trial is almost always a controlled clinical trial in which one group of research subjects is given the treatment or drug under investigation and another group of research subjects is given another treatment or drug or not given any treatment.

Phase III trials are usually the most expensive and extensive of the phases in drug development, today being conducted in multiple centres across the world. All drugs do not successfully reach the third phase of drug development. The new drugs that do pass through all three phases are prepared for marketing, for which approval is needed from the relevant regulatory body.

Phase IV

Phase IV trials that are also known as Post Marketing Trials test drugs that have already received marketing approval and are not new drugs (Angell 2004). There are different types of Phase IV trials that include: additional studies conducted to get further information on adverse reactions or side effects; long-term studies to investigate a drug's effect on morbidity and mortality; trials in a patient population that were not adequately studied in the phases prior to marketing; trials to support the drug's use for an approved indication (Levine 1988). Phase IV trials have been criticized for largely being used to find new uses of old drugs and enhancing market potential rather than investigating side effects of a drug (Angell 2004).

5. Cost of research and development

With no drug price control or regulation mechanism, in the U.S., prescription drugs are extremely expensive. The American public spends 200 billion dollars a year on prescription drugs and the figure is only increasing (Angell 2004:xx). Americans are taking more drugs today than they used to earlier and the drugs being prescribed today are likely to be costlier than older ones with pharmaceutical companies resorting to random price rises before a patent expires. For example, the drug company Schering-Plough, increased the price of its patented allergy medication Claritin thirteen times over a five-year period before the patent expired (Angell 2004).

High costs of drugs in the U.S. are justified by the industry because it claims high expenses for research and development. The reality however, argues Marcia Angell is quite different because actual R&D constitutes a minor portion of drug company budgets with most of the expenses being devoted to marketing and administration. A highly publicized and controversial study done by the Centre for Drug Development at Tufts University in the U.S., announced in 2001, that it costs the industry 802 million dollars to bring a single new drug into the market (Angell 2004: 41) with time costs amounting to half that amount (Glickman *et al* 2009). The Tufts University study is however contested by Marcia Angell who argues that the figure claimed by the Tufts University study is misleading and is used essentially to justify high prices of drugs. The amount claimed by the study, Angell states, refers only to the cost of developing new molecular entities or newly discovered or synthesized molecules that comprise a very small number of new drugs developed.

Although R&D figures claimed by the drug industry are contested and there is little transparency in how much is actually spent on innovative research as opposed to the industry's marketing expenditures – the clinical testing stage of drug development is undoubtedly the most expensive (Angell 2004). The R&D figures claimed by the pharmaceutical industry must be considered with caution however, as budgets of drug companies may include marketing expenses as part of their R&D costs. Angell's research indicates that in 1990, 36 percent of drug company revenues from sales were spent on marketing and administration costs (Angell 2004:12). This category of marketing that the industry ostensibly calls 'medical education' includes advertising, drug promotions, wooing patient groups and giving freebies to doctors to prescribe a particular drug (Angell 2004). This line of argument, is also supported by an increase in post-marketing Phase IV clinical trials that are conducted by companies to look for new uses of an existing drug and extend patent and marketing rights rather than focus on the actual purpose of a Phase IV trial which is to investigate long term side effects and other aspects that were not possible during trials of earlier phases (Angell 2004).

6. Profits of the global pharmaceutical industry

According to Fortune magazine's annual ranking of 500 of America's largest industries, ten drug companies in the U.S. ranked above all pharmaceutical industry other American industries in average net returns in 2001. In percentage of sales, the

had 18.5 percent compared to the average net return for all other industries, in the Fortune 500, that together comprised 3.3 percent of sales. During the economic slump in the year 2002, the ten leading pharmaceutical companies on Fortune 500 were still raking in huge profits – their combined profits amounting to 35.9 billion dollars, an amount higher than the profits all the other 490 businesses together that amounted to 33.7 billion dollars. In the year 2003, profits of drug companies fell to 14.3 percent of sales but this figure was still higher than the median figure of 4.6 percent for all other industries that same year (Angell 2004:11).

7. Lack of innovation: me-too drugs and their impact on clinical trials

Huge profits amassed by the pharmaceutical industry consistently since the 1980s, albeit lower today than in previous years, are still higher than other industries. These profits are however no indication of innovative research and medical breakthroughs. The biggest problem facing the industry today is a lack of truly innovative drugs that provide significantly greater benefit than existing drugs. Major breakthroughs in drug discovery occurred after World War II, in the 1940s and 1950s, when several antibiotics such as penicillin for the treatment of infections like syphilis and streptomycin for treatment of tuberculosis were discovered and patented by the pharmaceutical industry (Petryna and Kleinman 2006).

Drug companies and biotechnology firms are today struggling with a "drug drought" or "dry spell" in the drug pipeline (Bernard 2002:6; Macilwain 2011). The number of new approved compounds continues to remain stable in spite of an increase in R&D spending amounting to 30 billion dollars in the year 2001 (Bernard 2002:6). Drug companies are scouting research universities and medical centres across the world for drugs to license, and hope that progress in genetic research will bring the industry out of its current stagnant phase (Angell 2004). Large drug companies deceptively claim high R&D expenditures to woo politicians into diverting public funding for the early stages of drug development and to convince investors that there are potential innovative discoveries in the drug pipeline worth investing in—when in fact, the industry is struggling, with companies like Pfizer closing down its laboratories and laying off several thousand employees (Macilwain 2011).

Today, the industry's survival is dependent on the highly lucrative me-too drugs or those drugs that are similar to drugs already on the market. From the years 1998 to

2002 the U.S. Food and Drug Administration (FDA)—the country's main regulatory body authorized to protect the health of the public by ensuring the safety and efficacy of food, drugs, vaccines and medical devices and whose association with drug companies begins at the clinical trial stage—approved of 415 new drugs but of these only fourteen percent were true innovations or New Molecular Entities (NME)[2], and 77 percent were me-too drugs that were not significant improvements over existing ones (Angell 2004:75). In the years 2001 and 2002, only seven innovative drugs were given priority-review status by the FDA (Angell 2004: 55) because these drugs were proved to be significantly better than existing drugs.

The regulatory requirements of the U.S. also facilitate the drug company in its production of me-too drugs without questioning the commercial agendas of the industry. The FDA approves a new drug for its use and dosage. If a drug company tests a drug for a use marginally different from an existing drug of the same class and gets a patent, no other company can market that drug for that particular use. The usage can be very similar to the original existing drug. Phase IV trials are often done by companies to look for new uses of an existing drug and extend patent and marketing rights (Angell 2004). Furthermore, the FDA regulation requires a drug company to prove that its drug is better than nothing or a placebo rather than having to compare the new drug with a pre-existing one. Clinical trials are therefore often used to compare a me-too drug with a placebo, which makes it easier to prove superiority of the me-too drug over pre-existing drugs resulting in a preference for placebo use in clinical trials. If new drugs were required to be compared to existing ones in a clinical trial, fewer me-too drugs would be on the market and drug companies would have to focus on actually producing innovative drugs and fewer clinical trials would be conducted (Angell 2004).

- **Preferred diseases or conditions**

Me-too drugs capitalize on a profitable market that already exists and that has potential for expansion. These drugs, therefore, usually treat life-long conditions such as cholesterol, depression or high blood pressure. For example, the anti-depressant

[2] A NME or New Chemical Entity (NCE) is a molecule in the process of development, is not previously known to the FDA and it is not a version of a substance that has already been tested and approved. The development or synthesis of an NME or NCE is the first stage of drug development. It is the NCE that can be licensed to another agency to be developed into a drug.

medication, Prozac, produced by Eli Lilly, the first popular Selective Serotonin Reuptake Inhibitor (SSRI), that made annual sales of amounting to 2.6 billion dollars (Angell 2004:82) led to other companies—seizing the market opportunity created by Prozac—to develop similar SSRIs such as Paxil by GlaxoSmithKline and Zoloft by Pfizer (Angell 2004).

Me-too drugs are also used, as a way of extending the patent life of a profitable blockbuster drug that is about to go off its patent. The drug company develops a very similar drug to the one patented, calls it by a new name and convinces physicians and consumers that it is better than the drug just coming off patent or better than a competitors drug. For example, the drug Nexium to treat heartburn made by the drug company AstraZeneca, was brought on the market just as the patent for Prilosec, the drug company's blockbuster heartburn drug was about to end. AstraZeneca earned six billion dollars in a year from Prilosec and therefore an immediate replacement was necessary to prevent a generic manufacturer from producing a similar and cheaper drug after the patent expired (Angell 2004). The twenty-year monopoly granted to patents under TRIPS encourages producing more but not significantly beneficial drugs by tweaking or producing variations of old drugs, rather than fostering true innovation as is claimed by proponents of TRIPS (Tyfield 2010).

8. Disease priorities

Drug companies are commercial enterprises. Not surprisingly then, they prioritize investing in diseases or conditions that are lucrative. Diseases of impoverishment such as malaria, Tuberculosis (TB), sleeping sickness, diseases caused by parasitic worms, are not of primary interest to the pharmaceutical industry for the poor cannot afford expensive medicines (Angell 2004). Between the years 1975 and 1997, 1223 New Chemical Entities were commercialized but among these, only thirteen were meant for "tropical diseases" and only four of these were the results of research and development by the pharmaceutical industry (Lexchin 2001:1451). An analysis conducted on pharmaceutical-company sponsored trials registered under the U.S. trials registry between the years 2005 and 2007, indicated the largest number of registered trials in oncology followed by trials on disorders of the central nervous system such as sleep disorders, multiple sclerosis and attention deficit disorder. The numbers of trials for infectious diseases, particularly trials on bacterial diseases, were

found by the study to be declining. The numbers of early phase trials in this category were also found to be decreasing in numbers (Karlberg 2008).

The pharmaceutical industry's role in the popular dissemination of mental illness and the marketing of different drugs for specific disorders, as well as of life-style diseases, like male erectile dysfunction and obesity, clearly indicates where the industry's priority lies. When the third edition of the Diagnostic and Statistical Manual of Mental Disorders reorganized its classification of mental disorders and created new categories, the pharmaceutical companies catered their drugs and marketing strategies to the newly recognized conditions (Healy 2006). For example, the drug Xanax was tested in clinical trials for the newly recognized "panic disorder". The manufacturer, Upjohn, organized academic conferences around this new condition and engineered an environment of keen interest in panic disorders by academics and media alike. As "panic" entered the common lexicon, more people began to use the term to report their feelings, where earlier they would have described anxiety. Panic implied a biological problem needing a drug intervention, unlike anxiety that was perceived as a psychosocial condition that responded best to non-drug therapies (Healy 2006).

Adolescents were also targeted as a market for antidepressants such as Pfizer's Zoloft and Glaxo's Paxil. These companies ran clinical trials to market their antidepressants as only options to reduce risks of suicide due to depression. The clinical trials of both Paxil and Zoloft, however, indicated suicide rates among children—evidence of which is not indicated in the literature (Healy 2006). David Healy argues that data from clinical trials—that last for only six to eight weeks, for a condition such as depression that actually lasts for months and years—can only indicate that the treatment does have some effect and should be used as a basis for further, long-term research to prove that the treatment is actually working for the particular condition. Healy states that there is a common perception that clinical trials provide evidence that a treatment works but philosophically a clinical trial is based on a null hypothesis that a potential treatment is not different from a placebo. Clinical trials, he further argues are now being given a "centrality" in the medical market place and become tools of "therapeutic bandwagons" (Healy 2006: 78).

In 1999, about 325 million dollars were spent in the U.S. to advertise only four lifestyle drugs that included Viagra (Sildenafil) for erectile male dysfunction and

Xenical (Orlistat) for obesity (Lexchin 2001:1450). For the obesity drug Orlistat, there is no evidence that the drug is more effective than dietary changes in reducing morbidity and mortality due to obesity. These persuasive marketing strategies of drugs began to change the way people defined their behaviour for themselves and influenced the way is which the medical profession responded to a condition by prescribing the more lucrative drug therapy that could have been treated by using behavior therapy or some non-drug method (Lexchin 2001).

9. Bias in clinical trials

Clinical trials are used to establish the safety and effectiveness of drugs or treatments before they can be sold to the public. "Yet trials are imperfect and, at times, biased instruments that may or may not yield the most complete evidence about a drug's benefits and risks" (Petryna 2009:1). In other words, a clinical trial can be designed in ways to serve industry interests. For example, as discussed earlier on in this chapter, in a RCT the intervention being tested can be compared with a placebo instead of a known treatment for the same condition. A clinical trial that compares a new drug with a "sugar pill" is more likely to have a successful outcome than when it is compared to a known, effective treatment. Apart from using placebo, a clinical trial can also recruit younger trial subjects in order to create positive outcomes because younger trial participants are less likely to have side effects to a drug than older trial subjects. Another way to rig a clinical trial is to administer a lower dose of the older, comparator drug to make the new treatment seem more effective. In addition, companies do not always publish negative data that emerge from clinical trials as their position on the stock market can fall considerably. The FDA can do little to prevent the concealing of data by companies, even though attempts have been made by the International Committee of Medical Journal Editors to not publish trials that conceal negative results (Angell 2004; Petryna and Kleinman 2006; Petryna 2009).

II. In Search of Cheaper and Easier Options: India and the Globalized Clinical Trial

By the early 1990s, clinical trial sites had not only moved from academic medical settings into hospitals and private clinics but clinical trial operations also began to shift to non-traditional research areas such as Eastern Europe, Africa and Latin America. High infrastructure costs and a shortage of willing research subjects are among the main reasons for the outsourcing of clinical trials (Petryna 2005; Thiers, Sinskey and Berndt 2008). By the year 2004, almost 42 percent of all drug development related expenditures had been assigned to outsourcing compared to four percent in the early 1990s (Petryna 2005:193). Figures from the year 2005, suggest that 40 percent of all clinical trials that year were carried out in emerging markets (Lustgarden 2005:68 cited in Petryna 2009:13). In 2004, large pharmaceutical companies like GlaxoSmithKline operated 29 percent of their trials outside the U.S. and Western Europe, with an increase to 70 percent in the year 2006. In 2004, the other pharmaceutical giant Merck conducted half of its clinical trials outside the U.S., which was an increase of 45 percent since 1999 (Schmit 2005 cited in Petryna 2009:13).

The FDA also promoted the need for globalizing clinical research operations in the 1990s (Petryna 2005). In 1996, the FDA in collaboration with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) developed guidelines to harmonize and unify Good Clinical Practices (GCP) of the European Union, Japan and the United States in order "to facilitate mutual acceptance of clinical data by the regulatory authorities in these jurisdictions" (GCP 1996:5).

India and China have emerged as attractive options for clinical trial operations in the last four or five years. The FDA figures from the year 2006 on the number of clinical trial investigators enrolled with the agency show that Russia had 623, the largest number of investigators, followed by India who had 464 investigators, with 332 investigators in Poland and China had 307 investigators (Petryna 2009:13). In 2007, a study was conducted to analyze country and region-specific trends in the globalization of biopharmaceutical clinical trials. It used data from the U.S. clinical trial registry, which, had information on recruiting and completed studies in more than 140

countries, sponsored both by the public and the private sector (Thiers, Sinskey and Berndt 2008). The study found that although the U.S. had the largest number of clinical trial sites in the world followed by Germany, with the traditional clinical trial regions of North America, Western Europe and Oceania together comprising 66 percent of the trial sites of the world; the regions of Asia, Latin America, Middle East, Africa and Eastern Europe were found to be hosting 17 percent of actively recruiting clinical trial sites, with countries such as China and India having "grown rapidly from an almost negligible base in just several years" (Thiers, Sinskey and Berndt 2008: 13). The analyses also indicated that in terms of growth rates in recruiting biopharmaceutical clinical trials, 24 out of 25 of the fastest growing countries are located in the emerging regions. The authors of the study cite reasons such as the high average relative annual growth rates in recruiting clinical trials, combined with a low density of trials per population, investment in clinical research infrastructure, as factors that enhance the potential for countries like India and China "to grow into major players" in the clinical trial industry in the future (Thiers, Sinskey and Berndt 2008:13). Changes in patent laws and other domestic drug development laws as we see later in the section on India, have facilitated the growth of a clinical trial industry outside the West.

1. Reasons for the globalization of the clinical trial

Among the main reasons for the developed world moving its clinical trials to other countries are: a) high costs of conducting trials in the developed world, b) tedious regulatory requirements of the FDA c) the need to find large numbers of research subjects as quickly as possible.

While R&D figures for animal studies and laboratory research are contested, there is no disagreement on the huge investments required to test new drugs or treatments on human beings. Figures on R&D spending show an increase in the past three decades, from 1.1 billion dollars in 1975 to 44.5 billion dollars in 2007 – approximately 40 percent of this amount is spent on clinical trials by the ten leading pharmaceutical companies (Petryna 2009: 12). According to management consultants, A.T. Kearney, the cost of clinical trials can be two-thirds of the cost of developing a new drug but conducting clinical trials outside the U.S. and Western Europe can reduce costs from 30 to 65 percent, depending on the location (Kearney 2006).

The extremely expensive and time-consuming operation of drug development is made more tedious and slow for sponsors and investigators by the FDA's stringent regulations "that have become more and more complex, placing a greater burden on investigators in terms of compliance, documentation, and training" (Glickman *et al* 2009:816). Multinational clinical trial sponsors are therefore looking for locations where clinical trials are not just cheaper to run but quicker to complete. According to CenterWatch—an organization specializing in global clinical trial information—it takes an average of 68 clinical trials, 4000 patients, and 141 medical procedures per patient, before a product gains approval by the FDA (Bernard 2002: 8).

According to Stan Bernard, the president of a consultancy firm for the pharmaceutical industry, regulatory requirements are not the only reason "for slowing down product development". The drug industry also "shares the blame" because of its "inefficiency in recruiting patients into clinical trials" (Bernard 2002: 8). Recruiting large numbers of trial subjects is among the most costly and time-consuming aspects of running a clinical trial. When American prison populations were prohibited from participating in clinical trials, in the 1970s, U.S. trial sponsors lost their largest human resource for clinical research (Petryna 2005). The time spent in recruiting large numbers of willing trial subjects as well as retaining them until the very end of a clinical trial is a challenge. Losses could potentially amount to millions of dollars for each day a drug is delayed in getting on the market (Drennan 2003). Inefficiency in recruiting patients for clinical trials is said to cause 90 percent of the delays in development (Bernard 2002:8). Based on CenterWatch estimates, less than five percent of U.S. citizens comprising four to five million participate in clinical trials (Drennan 2008: 84)

Large numbers of research subjects are necessary for the Western pharmaceutical industry. Some of the reasons why clinical trials need a large number of research subjects include (Petryna 2009: 20):

- Many clinical trials are run to test the highly lucrative and competitive business of 'me-too' drugs that copy the blockbuster drugs and profit from markets that have already been captured. Since me-too drugs are so similar to pre-existing drugs, large numbers of trial subjects are required to produce statistically significant results to claim that the particular drug tested is superior than those that are similar and already on the market.

- The FDA requires trials to use large numbers of patients to prove long-term safety of drugs, especially if those drugs are meant for extensive use (Petryna 2009).

- Populations in the developed world are "treatment saturated" that is, they take too many drugs, making then unsuitable to participate in clinical trials due to the high possibility of drug-drug interactions that can affect obtaining accurate evidence on drug efficacy (Petryna 2009).

2. India as an attractive option for conducting clinical trials

By the year 2012, India is predicted to conduct nearly five percent of the world's clinical trials (Drabu, Gupta and Bhadauria 2011:1). Although India accounts for just 0.1 percent of the R&D budget of the U.S. pharmaceutical industry (Thatte and Bavdekar 2008:318), the U.S. National Institutes of Health clinical trial registry indicated that in January 2011, the number of clinical trials being conducted in India was 1506, which is the highest in the South Asia region followed by 157 clinical trials in Pakistan (U.S. National Institutes of Health 2011). Information on China, categorized in the East Asia region in the registry, indicated 1975 trials in the same period. Management consultants, A.T. Kearney, developed a Country Attractiveness Index for Clinical Trials to assess which countries outside the U.S. had the potential to become the most sought after global destinations for conducting clinical trials. India was rated second after China by the Kearney index whose assessment criteria for each country included: patient pool, cost efficiency, expertise, national infrastructure and the regulatory environment. Regarding patient availability, India scored higher than the U.S. on the Kearney index (Kearney 2006).

India is being increasingly perceived as attractive destination for conducting clinical trials "because of its genetically diverse population of more than one billion people who have not been exposed to many medications but have myriad diseases, ranging from tropical infections to degenerative disorders. Virtually all Indian doctors speak English, and many have acquired postgraduate qualifications abroad, primarily in Britain or the United States. Added to these attractions are cheap labor and low infrastructure costs, which can reduce expenditures for clinical trials by as much as 60 percent" (Nundy and Gulhati 2005: 1634).

The promotion of India as a suitable site for conducting clinical trials is the result of the combined efforts of a network of relationships governed by a host of procedures and regulations associated with a clinical trial. On the one hand are those sets of relationships concerned with the business of conducting the clinical trial: the multinational drug company or the trial's sponsor, the CRO or the service provider and manager of the clinical trial, the investigator who actually conducts the trial and the medical institution or clinical trial site. At the other end, are the state and its regulatory representative, the Drugs Controller General of India or the licensing body, and the ethics committee. External to these actors, but at the centre of the clinical trial operation is the research subject: an individual who will either receive the intervention being investigated in a clinical trial or who will be in the control group that will not receive the experimental treatment or intervention under study.

While the actors have different roles to play in the clinical trial process each works in tandem with the other (Sunder Rajan 2007). For the sake of clarity, however, each of the four main actors—the state, the CRO, the drug company and the research subject is discussed separately.

The state

Clinical trial operations in India are regulated by the rules of the Drugs and Cosmetics Act, the main statute that oversees the manufacture and distribution of drugs. The Drugs Controller General of India (DCGI) that functions under the Directorate General of Health Services (Ministry of Health and Family Welfare) is responsible for approving licenses for drugs and vaccines and permission from the DCGI is required before initiating a clinical trial. In 2005, Schedule Y of the Drugs and Cosmetics Rules was amended. The amendment significantly changed the nature and form of the clinical trial industry in India. For new drug substances discovered outside India, the foreign sponsor or agency—after providing data from Phase I trials—is now allowed to conduct Phase II and Phase III trials in India while they are simultaneously being conducted at other global trial sites. The Rules also state that the foreign agency can be granted permission to repeat a Phase I trial in India. Regarding Phase IV trials, the Rules state that these trials "may not be considered necessary at the time of new drug approval but may be required by the Licensing Authority for optimizing the drug's use" (Schedule Y, amended 2005, The Drugs and Cosmetics Rules, 1945). In other

words, the amendments have opened the door for all four phases of drug trials to be conducted in the country, replacing the previous law that forbade concurrent trials in India so that Indian research subjects were not the first to be exposed to the risks of a trial. The Central Drugs Standard Control Organization (Ministry of Health and Family Welfare) is also in the process of making it easier for foreign agencies to conduct Phase I clinical trials, the phase where a drug is introduced into the human body for the first time. The amendment to drug development regulations have therefore not just facilitated the entry of the global clinical trial into India, but have expanded the scope of clinical trials thereby putting at risk the lives of many more thousands of potential Indian trial subjects.

With the 2005 amendment to the Rules the number of clinical trials being conducted in the country increased substantially (Personal interview with C.M. Gulhati on 24.7.2010; Ravindran and Nikarge 2010). The Mumbai-based Center for Studies in Ethics and Rights have analysed the data on trials registered in India's clinical trial registry. From this they have found that in the year 2006 and prior there were 64 trials registered, compared to 425 trials in the year 2009 (Ravindran and Nikarge 2010).

Both the DCGI and the ethics committee are required to enforce Schedule Y of the Drugs and Cosmetics Rules and ensure compliance with ethical guidelines of the Indian Council of Medical Research (ICMR) and India's Good Clinical Practice (GCP) guidelines. In the context of an emerging global clinical trial industry in India, the DCGI—similar in function to the FDA—that was a "fairly peripheral" body within India's regulatory framework in the past few years "is now in the process of recreating itself as a serious agenda-setting organization" along with the Department of Biotechnology (Ministry of Science and Technology) by building the capability of human resources for conducting clinical trials with the vision of developing "clinical research as part of a wider initiative to make India a global biotechnology power" (Sunder Rajan: 2007: 71).

The DCGI has however been held responsible for several regulatory violations due to its failure to ensure adequate protocol review and monitoring of active trials. According to C.M. Gulhati, the editor of the Monthly Index of Medical Specialties, documentary evidence indicates that the DCGI in certain instances has approved a clinical trial without a thorough review of its protocol. For example, a letter written

by the DCGI to the CRO Quintiles Spectral India Limited, in the year 2002, stating that it had no objection to the clinical trial for the drug Herceptin and granting it approval indicated that a clinical trial protocol several hundred pages long was reviewed in a period of only six days (Gulhati 2010). An "industry friendly" DCGI is one of the reasons why foreign drug companies come to India (Personal interview with C.M. Gulhati on 24.7.2010).

The pharmaceutical industry

The year 2005, when India revised the Rules allowing foreign agencies to conduct concurrent phase clinical trials, was also the year when the country became compliant with the TRIPS agreement. The Federation of Indian Chambers of Commerce and Industry (FICCI) released its white paper on the clinical trial scenario in India in the same year. The focus of the document was the need for a "very strong patent law" to prevent generic drug manufactures from copying drugs already tested in clinical trials, the need to streamline clinical trial operations in the country, build capacity of investigators, and for both the government and the industry to create a "culture of global GCP [Good Clinical Practice] quality trials" (FICCI 2005).

The Indian pharmaceutical industry in a TRIPS compliant scenario is faced with many challenges while at the same time TRIPS also enhanced the country's position as a site for the global pharmaceutical industry to conduct its clinical trials. Some key issues for India's drug industry and its clinical trial operations in a post-TRIPS scenario include:

- With India's recognition of product patents as opposed to the previous process patents, the global pharmaceutical company has been given some assurance of protection of their intellectual property (Sunder Rajan 2007).

- The TRIPS-plus negotiations in regional and bilateral Free Trade Agreements with the European Union and other countries like Japan have serious implications for drug prices in India and the protection of human subjects in clinical trials. If the demand by drug companies for data exclusivity is accepted then India's generic drug industry will either have to wait till the exclusive period beyond the twenty-year patent period is over or will have to repeat clinical trials, exposing larger and unnecessary numbers of people to the risks of clinical trials (Hiddleston 2006; ExpressPharma 2010).

- Increasing pressure on the pharmaceutical industry and at the same time greater opportunities to participate in the post TRIPS global framework has led to mergers of Indian drug companies with multinational companies and also acquisitions of India's industry by foreign companies. The multinational pharmaceutical companies facing patent expiry of hugely profitable brand name drugs between the years 2010 and 2014 and troubled by the lack of true innovations in the drug pipeline are looking at sites for mergers and acquisitions as well as low cost contract manufacturing and research services to make new drugs (Rai 2008; Charlotte 2011; Angell 204). The Indian government's policy of 100 percent Foreign Direct Investment (FDI), has facilitated several takeovers and mergers of Indian drug companies in the recent years; the largest being the takeover of Ranbaxy in the year 2008 by Daiichi Sankyo from Japan for 4.6 billion dollars (*Times of India* Network 2010).

- The growing foreign presence in India's pharmaceutical industry, critics argue, will lead to an increase in the promotion of irrational combinations of drugs and focus on production of expensive drugs. Many of the patent applications filed in India's mailbox could be for new uses and forms of known molecules and not for innovations (George 2007).

- India's entry to the WTO and the barriers to reverse-engineering of patent drugs for the long period of twenty years has compelled Indian drug companies to explore the risky business of drug development, like the drug industry in the West. The clinical trial is therefore central to this new business framework, as a new drug cannot be developed without undergoing the phases for testing it on humans. "In other words, the Indian pharmaceutical industry has itself served as a spur to the CRO sector" (Sunder Rajan 2007: 71)

The CRO

The main role of the CRO is to manage and supervise a clinical trial operation and ensure the clinical trial sponsor that all the regulatory and ethical requirements of the clinical trial will be taken care of. India's growing presence in the global clinical trial context has led to an emergence of several multinational CROs—Quintiles Spectral (India), ClinRx, Max Neeman, Veeda Clinical Research—to name a few. Approximately one hundred CROs are believed to be functioning in the country (Sunder Rajan 2007), whose primary objective is to market India to clinical trial

sponsors as a friendly and efficient site for clinical trial operations and to build a streamlined regulatory framework to govern the clinical trial (Sunder Rajan 2007; Gulhati 2010).

The CROs "put a premium on time and speed. They assess the regulatory environments of prospective countries" in terms of how long it takes to get approval to start a clinical trial and the time taken to activate the trial (Petryna 2009:16). The selling point of these organizations is to ensure regulatory compliance with both Indian and International GCP guidelines and with procedural requirements for clinical trial applications to the DCGI. In addition to regulatory concerns, CROs also assist in recruiting patients for clinical trials, with some of them having agreements with hospitals to ensure a steady supply of patients. For example, in the city of Bangaluru, in the state of Karnataka, the CRO, Lotus Labs Pvt. Ltd. has a Memorandum of Understanding with St. Johns Medical College for running clinical trials (Maiti and Raghavendra 2007).

Contract Research Organizations are also building a network with independent ethics committees. Independent ethics committees are commercial bodies that are increasingly gaining importance in the global clinical trial industry because CROs need to contract quick and efficient ethical review services for clinical trials that are being conducted by private agencies external to medical institutions. A CRO can also form its own independent ethics committee. For example, the CRO Veeda Clinical Research Ltd. has its own ethics committee (Nagarajan 2011). Regarding the structure and formation of ethics committees, Indian regulations only mention the composition and quorum that ethics committees should follow and state seven members as the minimum number required for a committee. There are no other guidelines or rules on the criteria for forming an ethics committee and selecting its members and neither is there any central registry for ethics committees. Therefore, any group of individuals can establish an independent ethics committee that offers CROs and other agencies or independent researchers quick ethical review services for a fee. "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" (Nagarajan 2011:17) for an ethical review?

The CRO in India is attempting to create a predictable clinical trial environment in order to attract multinational sponsors to India for their clinical research operations. These organizations have entire departments devoted to global regulatory affairs, whose main concern and objectives is to get things done fast, to be completely aware of all regulations and to avoid delays in getting approvals. Dr. Anjali Ahuja from the CRO CliniRx explains that the CRO has "to ensure that you don't put off a sponsor because of DCGI delays and requirements". Approvals from the Drugs Controller General of India (DCGI) according to Dr. Ahuja, take about nine to eleven weeks "so sponsors have to be prepared because we don't want to lose them" (Personal interview with Dr. Ahuja on 29.10.2010).

The physician-investigator

In India, the investigator of a clinical trial is often the physician of the patient enrolled in the trial (Personal interview with C.M. Gulhati on 24.7.2010). The physician-investigator is therefore, more likely to be successful in recruiting patients into a clinical trial rather than a CRO or drug company representative. However, if the principal investigator is also the trial subject's doctor the question of a direct conflict of interest arises (see chapter three for conflict of interest), especially if physicians are paid a fee to recruit patients into trials. Inducements offered to physician-investigators are a matter of great concern as the doctor's personal interests could potentially override the welfare of the research subject. The physician-investigator is likely to focus on recruiting patients to meet the criteria of size of a clinical trial rather than considering the risks and benefits for the patient being selected. While government doctors are not officially paid for recruiting patients, there are accounts of financial and other inducements made to doctors working in public hospitals by drug companies as incentives to recruit large numbers of patients. Payment to private physician-investigators for recruiting clinical trial subjects is more overt—ranging from rupees 60,000 to 120,000 per patient (Srinivasan and Nikarge 2009). The financial incentive depends on the type of trial being conducted, for example, for oncology trials that take place over a longer period of time, payments are higher (Srinivasan and Nikarge 2009). In addition, to attractive incentives made to individual doctors, clinical trials sponsors also offer the institution or trial site a fee to run the clinical trial. For hospitals, starved for funds, especially in small towns, clinical trials have become an easy source of revenue. For example, journalist Jennifer Kahn, in her

article in *Wired Magazine* of the U.S., describing India as a "Nation of Guinea Pigs" discusses her visit to a hospital in the town of Sevagram in Gujarat, that was selected as one of 28 clinical trial sites in India by a German Pharmaceutical company, Boehringer Ingelheim, to test its stroke prevention drug on stroke victims. Although the hospital's physician-investigator and chairperson of its ethics committee were aware that the drug would have side effects with little benefit for stroke patients, the sum of 30,000 rupees offered to the hospital with its single room stroke ward of eight beds was enough reason to offer the institution to the German company to conduct its trial (Kahn 2006).

The clinical trial subject: Why is India vulnerable?

The Country Attractiveness Index for Clinical Trials developed by A.T. Kearney, cited India as having the highest enrollment rates—after China—of trial subjects outside the U.S. (Kearney 2011). There is little information in the public domain on why people participate in clinical trials and the disaggregation of the population who participate, but from media reports on ethical violations of clinical trials we know that trial subjects are largely India's poor, vulnerable and unsuspecting populations who are induced into trials by promises of free treatment, money for participation and overall care and attention from a physician-a luxury they cannot otherwise afford.

In clinical trials run by a physician-investigator, a patient's decision to consent to the clinical trial could be governed by the patient's implicit faith in the doctor's judgment of the patient's best interests–an essential element of the unequal nature of the doctor-patient's relationship (London 2007). The patient may also fear denial of treatment in case of refusal to participate in a trial. The physician-investigator of the Sevagram hospital, journalist Jennifer Kahn describes is "uneasy about his clinical success" because his patients never question him: ' "nine out of ten times," ' the doctor states, ' "the patient will just ask me to make the decision about the trial for him. So what role should I play? Am I a physician concentrating on what's best for the patient? Or am I a researcher interested in recruiting patients?" ' (Kahn 2006:2).

The asymmetry inherent to every doctor-patient relationship is further exacerbated in India's health care system, which is marked by regional and socioeconomic inequities and compounded by a lack of trained health care providers in both the public and private sector. Only one percent of India's GDP is spent on health (Reddy *et al* 2011:

760), with most of the country's health care system's resources being concentrated in urban areas. For example, the number of health care workers per a population of 10,000 in urban areas is 42, which is more than four times that of 11.8 in rural areas and the number of allopathic doctors in urban areas is 13.3 per 10,000, a figure that is three times larger than the rural figure of 3.9 (Rao *et al* 2011: 590). Even though the public sector is the main provider of preventive care services, 80 percent of outpatient visits and 60 percent of hospital admissions are in the private sector" (Rao *et al* 2011: 587). As a result millions of people—precisely four percent of the population—are forced into poverty every year due to 71 percent of health spending being out of pocket expenditure (Rao *et al* 2011: 587). At the other end of the health care spectrum is a range of health care facilities that offer the best possible health care to the few Indian's who can afford to pay and are also increasingly being sought by patients from other countries (Reddy *et al* 2011).

With health care expenses as one of the leading causes of poverty in India, for many patients and their families clinical trials hold the promise of the only option of treatment and perhaps even a cure. For example, the drug company promised trial subjects at the stroke prevention trial at Sevagram two free physical treatments for the trial's duration (Kahn 2006). In another report, in the *Week Magazine*, a 24-year old woman in Mumbai signed a consent form to participate in a trial in the hope of getting free treatment for multiple sclerosis for which she would otherwise have to pay the unaffordable sum of rupees one lakh a month. The Phase III trial however did not bring the young woman any relief or benefit (Krishnan 2010). On the other hand, if a drug does prove beneficial to a patient in a trial it is most likely that the trial subject will not be able to afford the drug after the trial is over. The physician-investigator at the Sevagram hospital, for example, was also responsible for another trial to test an anti-clotting drug, Reviparin. The drug, at the cost of eight hundred rupees a day, the doctor said would not be affordable to his patients for whom snakebite and insecticide poisoning are major health concerns (Kahn 2006).

Individuals may also consent to a trial to earn an extra income (see chapter three for professional subjects). An article in the *Times of India* (June 18, 2011) indicated that women trial subjects were promised financial inducements to participate in an illegal trial to test a breast cancer drug. The women claimed to be paid rupees 9,000 for three

rounds of tests—a fairly substantial sum for the women said to be farm workers. The article also stated that in case the women experienced complications or there were abnormalities in their blood samples, they were paid rupees one thousand and asked to leave the trial site. The drug company is alleged to have not provided the women any information on the kinds of interventions that they would have to undergo in the course of the trial (*Times News Network* 2011).

Critics of the current clinical trial scenario in India, like Samiran Nundy, consultant at Sir Gangaram Hospital and C.M.Gulhati state three main reasons for their opposition to the global clinical trial industry in the country. Firstly, "the much-hyped earning potential is likely to remain a distant dream" because for example, in the year 2004, the U.S. spent 33 billion dollars on drug research while in India U.S. and other western companies combined spent only 30 million dollars (Nundy and Gulhati 2005: 1635). "Even with relaxed rules, India makes as much in one day by exporting computer software (which offers no direct risk to anyone's health) as it can in a year by offering its citizens as study subjects" (Nundy and Gulhati 2005:1635). Secondly, the Third World is being used as an experimental ground for testing the efficacy and safety of drugs that are neither safer nor more effective than existing drugs and also likely to be more expensive and therefore inaccessible to poor patients. Thirdly, drug companies or sponsors of drug trials afford little guarantee regarding affordability of new drugs tested in India (Nundy and Gulhati 2005).

Building a stringent regulatory environment

For the CRO, who is the link between the western sponsor and the clinical trial site it is important to challenge critics of clinical trials and create a positive image for India's clinical trial industry. While there are great advantages for the western drug companies to outsource clinical trials in terms easier and quicker subject recruitment and low costs, the reputation of India being weak on implementing clinical trial regulations and protecting its trial subjects would have a negative impact in convincing a global drug industry to come to India. The main concern for multinational drug companies is to ensure the integrity of clinical trial data and its "portability" "from anywhere in the world to U.S. regulatory settings of drug approval" (Petryna 2009:32). The concerns, therefore, around clinical trial regulations and ethical conduct of a clinical trial are based primarily on the kind of data collected

and whether it will be accepted by the American drug approval process. The CROs who are the largest and most profitable sector in the clinical trial industry in the West (Petryna 2009), in India too are "the most immediate beneficiaries of trials" (Sunder Rajan 2007:70). The CRO is therefore eager to ensure the sponsor that the trial conducted in India will comply with International GCP Guidelines and adhere to domestic clinical trial rules, which are in fact stringent, contrary to popular misconception about lax regulatory environments in the third world. The state too is working streamline the existing regulatory framework for clinical trials in India and efforts are being made to create an umbrella body that is invested with greater authority than the DCGI to regulate biomedical research in the country (Sunder Rajan 2007).

Conclusion

The discussion in this chapter indicates that clinical trials being conducted today are essential components of a vast business model. The context of the global clinical trial is complex and nuanced where common interests dictated by an entrepreneurial framework of profit connects different actors. It is about the multinational drug industry expanding its business by taking advantage of a populous nation with millions of easily available, treatment naïve people who live in poverty and in poor health. The global clinical trial is also about the actors of the host country eager to comply with the demands of the clinical trial industry (Petryna 2009).

An interest in creating a rigorous regulatory structure by both the state and the clinical trial industry is, however, devoid of serious ethical concerns that raise questions such as: who are the people being selected for the clinical trials and how are they being selected? Are drug companies interested in India's public health problems? Will the trial subject be able to afford a beneficial drug after the trial is completed and if the answer is in the negative then what are the advantages for the research subject? Is the state concerned about ensuring the health of its population or is it interested in the promise of FDI?

Chapter Two

A Review of Literature

Introduction

The discourse on ethics, ethical guidelines and ethics committees in the context of clinical trials is intrinsically entwined with the history of criminal acts and violations carried out in the name of medical experiments, and society's response to them. Abhorrent medical experiments justified in the name of scientific progress are not an anomaly confined to the methods used by physicians in Nazi Germany, but also include horrific acts committed on vulnerable research subjects by governments in many other parts of the world. Public pressure, high costs and stricter regulation of clinical trial practices in Western countries led to the expansion of the global pharmaceutical industry's operations to the developing world. This in turn led to the emergence of new arenas rife with the potential for exploitation of even more vulnerable people. Institutional ethics committee have their origin in this murky history. In order to understand why they were first considered necessary, and their continued significance and role in biomedical research one must trace the history of unethical clinical research, the resulting regulatory structures that emerged and the clash of interests between the architects of ethical guidelines for human subject protection and the drug industry.

Prior to World War II, there were no ethical guidelines for medical research using human subjects and ethical oversight was largely the responsibility of the individual investigator (Levine 1999; Baader *et al* 2005). The idea of establishing an ethics committee to protect human research subjects has its roots in the inquiry into the ethics of human experimentation that emerged in the aftermath of World War II when the world was horrified by the brutality of Nazi war crimes (S.R.G 1969) conducted apparently in the interest of scientific research. A little later, in the 1950s, a substantial increase in government funds for medical research in the U.S., led to a greater number of experiments using human subjects in that country. In time it emerged that some of these experiments were also conducted with scant regard for human dignity and safety – and today they are viewed as landmarks in the history of the development of ethics in human subject experimentation. The use of public funds for these experiments eventually led to a demand for public accountability, and for

protocols on how the interests of different actors in an experiment – the subject, the investigator and the scientist, could be "defined, protected and controlled" (S.R.G 1969: 6). Enquiries into unethical medical experimentation during the War years as well as investigations into the questionable ethics of experimentation in the 1950s and 1960s in the U.S. resulted in an awareness about the need to regulate the conditions under which human experimentation might take place while simultaneously maintaining the scientific integrity of research (S.R.G 1969).

The literature on the importance of an independent ethical review of clinical research can be been divided into three categories: firstly, unethical human experimentation that demanded the need for ethical review, secondly, the articulation of ethics committees in both international and national regulations and ethical guidelines and thirdly, literature on the role and functioning of institutional ethics committees whose primary mandate is to protect the welfare and interests of the clinical trial subject. Based on these categories of literature, this chapter is divided into four sections with the first three sections focusing on global literature on the subject of human experimentation and ethical review. The first section discusses some landmark unethical medical experiments with specific reference to the use of human subjects in Germany, Japan and the United States. The second section discusses the development of twentieth century international regulation for the ethical conduct of clinical trials—as an outcome of unethical human experimentation—and the emergence of guidelines specifically concerned with ethics of the global clinical trial. The third section discusses studies conducted on institutional ethics committees. The fourth section focuses specifically on the Indian context with examples of unethical experimentation of drug-company (both Indian and multinational) sponsored clinical trials and those funded by other private agencies. The global content of this chapter, particularly on the institutional ethics committee and its regulation has a primarily U.S. focus as most of the literature on the subject of ethics committees is from American sources. There is limited literature from India on ethics committees and the context in which ethical guidelines for human subject protection were conceptualized and developed here.

The process of conceptualization for the study on IEC members of selected hospitals in New Delhi was guided by the review of literature on the subject. This chapter also discusses the research objectives and the methodology of the study on IEC members.

I. The History of Unethical Human Experimentation in the Twentieth Century

1. Biological warfare experimentation in the War Years, 1933-45

The war years, 1933-45, were notorious for the large-scale, inhuman, experiments conducted by Germany, U.S. and Japan to test harmful biological warfare agents on their armed forces, prisoners of war and other vulnerable populations. In Germany, chemical warfare experiments—those that tested the effects of mustard gas and other chemicals on body parts—that were first conduced on animals were continued on army cadets who were given monetary incentives for their participation by the German army. Similar experiments were performed on concentration camp prisoners who were made to inhale phosgene, another kind of poisonous gas that resulted in death due to lung oedema (Baader *et al* 2005). The dynamics of experimental research during these years were marked by collaborations between research scientists and the military (Baader *et al* 2005). The military required knowledge on human endurance and it sought the support of Germany's scientific elite in conducting experiments to provide the necessary data. For the Japanese empire (1930-1945), Manchuria was the main site for conducting their biological warfare research or testing poisons and gases on humans. The Japanese also used the local inhabitants of Manchuria for their research on cholera, plague and frostbite. The Manchurians who resisted Japanese occupation became experimental subjects who were exposed to the cold for long periods, to contaminated water and other inhuman experimental conditions (Baader *et al* 2005). A Japanese army unit—Unit 731—whose main concern was protecting Japanese soldiers from disease is believed to have caused the death of about three thousand trial subjects during experiments in a period of ten years (Baader *et al* 2005:221).

The U.S. was different from Japan and Germany in the use of human subjects. They used their own populations such as prisoners, institutionalized children with disabilities, African Americans, women and other unsuspecting or vulnerable populations otherwise known as "subjects of convenience" (Baader *et al* 2005: 224). The Presidential Advisory Committee established in the U.S., in 1994 to investigate human radiation experiments conducted during the war years found that between the years 1944 and as late as 1974, the U.S. government supported about 4000 radiation experiments that used over 20,000 subjects (Josefson 1996: 1421). The captive

population of prisoners were the most popular research subjects with documentation on the use of prison populations as subjects for wartime experiments in the U.S. available from the year 1914. Prisoners were recruited for army-endurance experiments to test whether soldiers could effectively perform their duties under the influence of drugs (Hoffman 2000). They were also made to participate in federally sponsored research on encephalitis, gas gangrene, blood typing and malaria for which hundreds of prisoners were exposed to mosquito vectors (Baader *et al* 2005: 227).

2. Experiments on concentration camp prisoners in Nazi Germany

Physicians in Nazi Germany forcibly conducted a range of risky and often fatal medical experiments on concentration camp prisoners.

- **Hypothermia experiments**

In the years 1942-43, the concentration camp at Dachau was the site for hypothermia experiments to understand the human body's endurance of cold weather conditions. The experiments required prisoners to be immersed—some of them naked—in ice cold water. According to the Dachau Comprehensive Report, the trial subject's body temperature continued to fall even after removal from the extremely cold conditions. This drop in temperature is believed to have been the cause of death of many prisoners (Berger 1990).

- **Infectious disease experiments**

Experiments on malaria—as a result of which several prisoners died or suffered severe disabilities—were also conducted in Dachau to investigate immunization and treatment. For these experiments, over one thousand healthy prisoners were exposed to mosquitoes or were injected with mucous gland extracts of the malaria vector (United States Holocaust Memorial Museum). Prisoners across camps were also infected with yellow fever, small pox, and cholera germs to observe the course of a disease resulting in the deaths of hundreds of camp inmates (Hoffman 2000).

- **Sterilization experiments**

Sterilization experiments were conducted at the Auschwitz concentration camp under great secrecy and were performed by using either radiation or by injecting caustic substances into the uterus. The injection method, that was extremely painful and required injections at repeated intervals, was given to women under the guise of a regular gynecological examination. These experiments were conducted on primarily Russians, Polish and Jewish prisoners–defined as non-Aryans and therefore perceived

as enemies of the German state. The objective of the sterilization experiments was to prevent contamination of the Aryan population by non-Aryans and this was to be achieved by curbing reproduction of non-Aryan people while at the same time exploiting them as slave labour for war efforts (Benedict and Georges 2006). The women who were targeted for sterilization were usually unmarried and under the age of 50.

3. The historical antecedents of Germany's sterilization experiments

Sterilization experiments that dehumanized the human subject were largely driven by prevalent eugenic ideologies of racial hygiene or racial purity, and the study of genetic pathologies promoted by the German state and supported by the medical fraternity (Baader *et al* 2005; Mathuna 2006). The eugenic movement founded by the English scientist Francis Galton (1822-1911) subscribed to the idea that natural or biological laws govern the physical and non-physical aspects of all human beings. The eugenicists believe that through the biological processes of inheritance and the natural selection of ' "good genes" ' (Mathuna 2006: 5) only the strong and the intelligent would emerge as the worthy winners in the battle for survival in society. These morally advanced human beings, according to the proponents of eugenic ideology, would have the right to live a life of human dignity—as opposed to a world view that subscribes to all human beings having an equal chance to a dignified existence (Bruinius 2006; Mathuna 2006). The eugenic notion of improving the human race by selective breeding and involuntary sterilization of 'undesirable' sections of the human population has its foundations in the United States in the early decades of the twentieth century. Population control of those deemed 'unfit' and 'undesirable' first began with criminals and was then expanded to other social outcastes. The feebleminded were described as those individuals whose congenital mental deficiencies may not be obvious but were those people who lacked a moral conscience and were prone to promiscuity. These attributes of feeblemindedness were seen as the main causes of poverty and crime and the most efficient method to stop this blight on humanity was sterilization. Several American states adopted legislations giving them the authority to sterilize genetically flawed U.S. citizens (Bruinius 2006). The state of Indiana implemented the world's first sterilization law in the year 1907, that set the stage, for the U.S. to become the forerunner of state led support for sterilization of society's unwanted. California enacted its sterilization law in the year

1909 that resulted in the sterilization of more than 2,500 people in the first ten years of the enactment—the highest figure among all states (Bruinius 2006:10). Fifteen other states also passed sterilization laws, however state courts, rejected seven of these rulings. When the Eugenical Sterilization Act of Virginia was passed in 1927, the Virginia Colony—initially an asylum for epileptics and the mentally retarded and later for all poor and uneducated white residents of Virginia—selected an inmate, Carrie Buck, to test the legality of the sterilization law so that its proponents could challenge their beliefs in the higher courts of justice. Carrie Buck was in Virginia Colony because Dr. Bell and others believed that she was "feebleminded" and mentally deficient. "A defect in her genes made her unusually promiscuous..."and prevented Carrie and her mother from being "productive, law-abiding citizens" (Bruinius 2006: 5). Carrie, it was believed, would pass on her defected genes to her illegitimate child (Bruinius 2006). Carrie, however, was neither feebleminded nor mentally retarded but a victim of extreme poverty and social exclusion, institutionalized like her mother, so that society could rid itself of the nuisance and shame of poverty. In the Buck v. Bell case, the U.S. Supreme Court proclaimed a majority decision in permitting the sterilization of Carri Buck by Dr. Bell in 1927, without her consent. The Buck v. Bell case set a new precedent in eugenic history. After 1927, thirty states in the U.S. passed sterilization laws that also became the model for similar laws in other countries. The sterilization law enacted in the year 1933, by Adolf Hitler's National Socialist Party was based on the American sterilization ruling (Bruinius 2006).

Nazi physicians considered American eugenicists innovators in the field of racial purity. Influenced by the American example of sterilization, Nazi doctors initiated sterilization drives on a massive scale resulting in the death of thousands of concentration camp prisoners—a genocide that reached its height in the late 1930s. After the war, Nazi physicians who were tried in the German city of Nuremberg during the Doctors' Trials in 1946-1947, justified their sterilization experiments and eugenic beliefs by citing the example of their American eugenic predecessors. The Nuremberg Code, as we will see later in this chapter, was the outcome of deliberations in the trial of Nazi physicians for conducting heinous and risky medical experiments on individuals with reduced autonomy. The prisoners were coerced into participation in experiments. Their lack of freedom to give consent or refuse

participation in the experiments led to two essential elements of the Nuremberg code: the imperative of obtaining informed consent from an individual before conducting a clinical trial and the right of the individual to revoke consent in the course of research. The forced sterilization of thousands of U.S. citizens by American doctors, with state sanction and supported by the American elite is given little mention by American historians because of its association with Nazi Germany's eugenic history. The American desire for racial purity was however, as great as that of Nazi Germany, a historical fact that has been obscured by the revelations of the horrors of the Nazi holocaust (Bruinius 2006) and the subsequent outrage it caused.

4. Human experimentation in the U.S. after World War II

- **Prison populations**

Prisoners continued to be the most favoured population for medical research in the U.S. even in the years after the War. In the 1950s, the majority of Phase I trial participants in the U.S. were prison populations and in the year 1969, prisoners were used to test 85 percent of all new drugs (Hoffmann 2000: 2) across forty-two prisons in the U.S.

Prisoners were research subjects for a range of clinical trials, from cosmetic substances to psychological warfare agents and radioactive isotopes. With increasing exposés on prisoner abuse in medical research, a moratorium was placed on prisoner experimentation that eventually led to legislations by the U.S. Department of Health and Human Services (HHS) in the year 1980 that limited the use of prison populations in biomedical experiments (Hoffman 2000, Petryna 2009). The legislation caused a significant decline in the human subject pool for the research community who at this time began to expand its clinical research activities to countries like Sweden and the United Kingdom (Petryna 2009).

- **Thalidomide, 1960s**

Another landmark case in the history of unethical human experimentation and one that made front-page news in the U.S. media was the use of the drug Thalidomide as a sedative and as treatment for nausea for pregnant women. The drug was put on the market in the year 1957 by a West German drug company and by the 1960s it was sold all over the world including the U.S. The American drug company Richardson-Merrell pharmaceuticals sought approval from the FDA to market Thalidomide

without undergoing appropriate pre-clinical tests on pregnant animals and clinical research on women. Not long after Thalidomide was marketed, it was found to cause severe deformities in infants, with reports of about ten thousand children across forty-six countries suffering from abnormalities due to the drug. In 1962, the U.S. Congress in response to the disastrous effects of Thalidomide passed the 'Kefauver Amendments' to the Food, Drug and Cosmetic Act, that, for the first time required drug manufacturers to prove not only safety of the drug but also the effectiveness of their products before marketing them. This new rule institutionalized the controlled clinical trial methods of randomization and double-blinding[3] patients as a necessary condition to prove drug effectiveness and for approval to marketing a new drug (Petryna 2009).

- **The Willowbrook hepatitis study, 1956**

In the year 1956, a study was funded by the U.S. government to investigate the natural course of the infectious hepatitis A virus in children institutionalised in the Willowbrook State School for mentally challenged children in New York. The children who suffered from the most severe retardation and behavioural disabilities were injected with the virus preparation. The study that continued for over a decade was justified by one of the investigators, Saul Krugman, on the basis of the fact that Willowbrook routinely suffered from epidemics of all kinds of diseases including hepatitis and the children might become infected with the disease in any case. The risks that the children were exposed to were, therefore, believed by the proponents of the study to be fewer in the controlled conditions of the experiment (Krugman 1986; Petryna 2009).

- **The Tuskegee syphilis study, 1932-1972**

Another unethical experiment that horrified the American public and the rest of the world was the research study sponsored by the U.S. Public Health Service to study the effects of untreated syphilis on 400 African American sharecroppers in Tuskegee, Alabama over a period of forty years. The control group for the study were two hundred men who did not have the disease. At the start of the study in the 1930s there was no known treatment for syphilis but by the 1940-50s, penicillin was widely known to be an effective cure as well as being easily available. Despite this knowledge, the study continued as an observational study to understand the natural

[3] Clinical trials are usually double blinded, which means that neither the trial subjects nor the researchers know which trial subjects receive the experimental product (Petryna 2009)

course of the disease. The men were denied existing treatment that led to many deaths (University of Nevada, Office of Research Integrity—Human Subjects Research; Baader *et al* 2005; Petryna 2009). The investigators of the study believed that they did nothing wrong but were "merely observing the effects of a sexually-transmitted disease in a population notorious among whites for its ' "sexual depravity and license" ' (Baader *et al* 2005: 225). The justification for this study "may explain why investigators at the Public Health Service and later, the U.S. Centers for Disease Control, continued to prove unable to recognize the ethically-questionable nature of this research" (Baader *et al* 2005: 226).

- **Syphilis experiments in Guatemala, 1940s**

In a rare admission of state sanctioned atrocities against vulnerable and unsuspecting human subjects in research, the United States government apologized in the year 2010 —sixty-four years after the fact—to victims and survivors who were deliberately infected with syphilis in an experiment conducted in the 1940s by a physician employed by the U.S. health service. The physician John Cutler—who in the 1960s joined the Tuskegee Syphilis study—used 696 subjects including male prisoners and male and female patients from the national mental health hospital to study if penicillin was effective for prevention in the early stages of syphilis. Prostitutes who had syphilis were used to infect the prisoners with the disease. The research team did not seek consent from trial subjects and only obtained permission from institutional authorities. Human rights activities in Guatemala are in the process of seeking compensation from the U.S. government for the victims and their families, but it is not clear when and if the compensation will be given (McGreal 2010).

II. Regulation for the Ethical Conduct of Clinical Research

With increased public and political response to the repercussions of unethical medical experiments, formal ethical codes and regulations for protecting research subjects developed across nations after WW II. The Nuremberg Code that was formed in the aftermath of Nazi war crimes was the first fundamental set of principles in the history of the ethics of medical research. Other ethical guidelines for the protection of human subjects in clinical research such as the Declaration of Helsinki were built on the principles laid down by the Nuremberg Code. The ethical guidelines developed by the Council of International Organizations of Medical Sciences were conceptualized specifically for research conducted in developing countries by wealthier nations.

These guidelines for the protection and welfare of clinical trial subjects also developed special considerations for research on vulnerable populations such as children and pregnant women and those with reduced autonomy such as prisoners and the mentally challenged. Some of these ethical guidelines, particularly the Declaration of Helsinki, have been expanded and revised over the years particularly as the scope of clinical research has widened and the global clinical trial has raised new ethical dilemmas and questions. For example, what are the kind of health interventions that should be tested on Third World populations and should people living in low-resource settings be given treatments that are inferior or different to the ones used by populations in the developed world are on going debates that will be discussed in this chapter and in chapter three.

1. The Nuremberg Code, 1947

The extent of the atrocities committed by Nazi physician-researchers in the name of science became public during the International Military Tribunal in 1946—convened by the allied forces of France, U.S., Great Britain and the Soviet Union—in the German city of Nuremberg. The Doctor's Trials in the years 1946-1947, that focused specifically on the gruesome nature of medical experiments conducted by physicians on concentration camp prisoners was held under the authority of the American judiciary. In August 1947, American judges of the Doctor's Trial together with American physicians established ten rules—the Nuremberg Code—for physicians to follow for the protection and welfare of the research subject (Grodin and Annas 1996).

The essential principle recognized by the Nuremberg Code was the imperative of voluntary informed consent from the subject. It states:

> Voluntary consent of the 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, the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision (The Nuremberg Code cited in *The Journal of the American Medical Association* (JAMA) 1996: 1691)

During the trial deliberations, the American physicians referred to the Hippocratic oath that obligates physicians to protect patients from harm in the course of treatment. However, they also stated that the Hippocratic oath was not adequate for protection of human subjects and that there was a need to define a set of principles that would focus on the rights of the individual subject. While the Hippocratic oath stresses the need to protect the patient it does not consider the autonomy of the patient who has no choice but to trust the judgement of the treating physician. Further, the Hippocratic oath does not offer guidance on the protection of the research subject who might face risks that are greater and different than the patient in the course of an experiment and should therefore have the right to consent or refuse participation in a trial. The Nuremberg Code, therefore, in addition to the principle of informed consent also introduced the right of a research subject to withdraw from the trial at any point (Shuster 1998).

The Nuremberg Code granted autonomy to the individual as well as made rules for physician-researchers (Shuster 1998) requiring them to ensure that the rights of the subject never supersede the risks involved in scientific research and that experiments be conducted for the benefit of society:

> 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 (The Nuremberg Code cited in JAMA 1996: 1691)
>
> The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury (The Nuremberg Code cited in JAMA 1996: 1691)

The Nuremberg Code—the first set of explicitly laid down principles for human subject protection on biomedical research—was, however, marginalised soon after it was established. Medical organizations distanced themselves from the Nuremberg Code that was wrapped in Nazi horror. They did not want to be judged by standards that applied to "barbarians" and not "civilized physician-investigators" (Katz 1996:1663; Shuster 1998).

The Nuremberg Code did not distinguish between healthy research subjects and patients whose consent was rarely taken by the physician-investigator. Many scientific researchers frequently fail to distinguish between two distinctly different relationships: with that of the patient, where there is an obligation of treatment and the

research-subject, where the obligation is to a protocol being followed to prove a hypothesis. Clearly defining these relationships is however important because if research is confused with treatment then the rights of the individual subject can be affected (Grodin and Annas 1996).

The Nuremberg Code also fell short of addressing other questions of human experimentation in the Nazi era. For example, it did not challenge the questionable relationship between the physician and state and the pressures exerted by the state on its medical community. It did not question the role of the physician as the state's instrument in selecting those populations—Jews, gypsies, homosexuals, disabled and Slavs—deemed undeserving of a life of dignity (Grodin and Annas 1996).

The Nuremberg Code was largely the result of the American judiciary working together with American physicians to bring justice to victims of medical experiments, and to draw a plan for subject protection in future research. Ironically, soon after the Nuremberg trials, it is the U.S. that witnessed ethical violations in medical experiments, in which, vulnerable American citizens such as prisoners, mentally challenged children and racial minorities were identified as convenient and easy to target subjects for clinical research.

2. The Declaration of Helsinki

Not long after the declaration of the Nuremberg Code, in 1947, the World Medical Association (WMA), an international organization of physicians was formed. Its objective was to achieve the highest ethical standards in medicine and professional conduct. In the aftermath of war crimes and unethical experimentation on human subjects, the WMA proposed the establishment of international ethical guidelines for physicians to follow anywhere in the world. In 1964, at the 18th General Assembly in Helsinki, Finland, the WMA delivered the Declaration of Helsinki: Ethical Guidelines for the Protection and Welfare of Human Subjects in Biomedical Research (WMA 2011).

The tenets of the Declaration of Helsinki went beyond the Nuremberg Code to include the specific responsibility of the physician in protecting human subjects in clinical research (Williams 2008).

> It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The Physician's knowledge and conscience are dedicated to the fulfilment of this duty (WMA Declaration of Helsinki 2008).
>
> The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent (WMA The Declaration of Helsinki 2008).

It also widened the understanding of informed consent as laid out in the first principle of the Nuremberg Code by including the idea of proxy consent in the case of minors and those mentally or physically incapable of giving consent (Levine 1988).

The Declaration of Helsinki has been revised six times since its inception, the latest being in the year 2008. It was in the 1975 revision—and in subsequent revisions—when the Declaration of Helsinki first stated the need for an ethics committee for the protection of human subjects in clinical research (Levine 1988):

> The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins...It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies (WMA Helsinki Declaration 2008).

In the year 2000, the fifth revision of the Declaration of Helsinki, made another significant change to international ethical guidelines. The revision was the result of considerable debate in the research community on the ethics of using placebo, in clinical trials in the developing world, for the control or comparator group in a RCT when a known effective therapy exists. The use of placebo in research when there is an effective treatment may be ethically problematic in the West (Glickman *et al* 2009) but proponents of placebo use argue that it is not unethical to have placebo controlled trials in the developing world because the international standard of care is too costly to be implemented and sustained in developing nations. The debate on placebo use and the resultant revision of the Declaration of Helsinki is widely discussed in the literature on the subject and one that merits further discussion.

- **The fifth revision of the Declaration of Helsinki and the debate on placebo use**

From the 1990s, the globalization of clinical research and the search for trial subjects in less wealthy nations has led to considerable literature about ethical oversight with specific regard to the protection and welfare of trial subjects in these countries. "Given the emphasis on time, speed and profitability" anthropologist Adriana Petryna expresses particular concern with how scientific integrity is maintained and ensured in these "new clinical trial frontiers" (Petryna 2009: 17). In developing countries "wide disparities in education, economic and social standing, and health care systems may jeopardize the rights of research participants" (Glickman *et al* 2009:818). Moreover, "there may be a relative lack of understanding of both the investigational nature of therapeutic results and the use of placebo groups" (Glickman *et al* 2009: 818).

The debate on the use of placebo was provoked by the outcomes of HIV clinical trials conducted in the developing world in the 1990s. Fifteen clinical trials were conducted across different parts of Africa to test the simpler and shorter regimen or short course AZT (Zidouvidine) treatment to prevent mother-to-child transmission of HIV. The U.S. Government sponsored nine of these fifteen studies through either the National Institutes of Health or the Centers for Disease Control and Prevention (Lurie and Wolfe 1997). The crux of the controversy of these HIV trials was the use of a placebo arm or no treatment even though an effective standard of care–the 076 AZT protocol was known (and used in the West) to reduce mother-to-child transmission of HIV infection by almost seventy percent. Over 12,000 HIV infected women were used for the trials described as "a watershed in the debate over ethical standards in global clinical research" (Petryna 2005:4). By depriving women trial subjects of this treatment, about 600,000 infants were born to mothers in the African continent with HIV in 1997 (Del Rio 1998:328).

Responses to the use of placebo in these HIV trials were polarized. In 1997, Peter Lurie and Sidney Wolfe argued in their essay in the *New England Journal of Medicine* that the research was unethical since effective medicine was available but was not used. They argued that an "acceptance of a standard of care that does not conform to the standard in the sponsoring country results in a double standard in research. Such a double standard, which permits research designs that are unacceptable in the sponsoring country, creates an incentive to use as research

subjects those with less access to health care" (Lurie and Wolfe 1997: 855). The essay led to widespread discussion on the ethics of conducting research in the developing world and the responsibility of sponsors and investigators towards clinical trial subjects (Wolinsky 2006). Marcia Angell in her editorial, also in the *New England Journal of Medicine*, likened the HIV trials to the highly questionable ethics of the Tuskegee trials as the trial subjects were denied known treatment (Angell 1997).

Proponents of the trials argued that a placebo had to be used to establish the effectiveness of the simpler regimen because the standard of care, or 076 Zidovudine regimen, has a complex protocol that would not be feasible and sustainable in the context of dysfunctional healthcare systems and economic realities of developing nations. (Del Rio 1998). The 076 protocol requires women to be tested for HIV early in their pregnancy for them to receive the treatment. It also has to be continued after childbirth and requires intravenous and oral administration of AZT. In addition to the tedious regimen, the proponents of the trials argued, the costs of the standard of care—800 dollars for mother and child—were prohibitive for health care systems in the developing world and the short course regimen costing eighty dollars in comparison was the more practical treatment option for them (Resnik 1998). David Resnik from the department of medical humanities in the East Carolina University School of Medicine in the U.S. argued that "the use of placebo-controls in these trials can be justified on scientific and moral grounds, and that standards of ethical research on human subjects are universal but not absolute: there are some general ethical principles that apply to all cases of human subject research but the application...of these principles must take into account factors inherent in a given situation..." (Resnik 1998: 288). Critics like Joe Thomas, from the Chinese University in Hong Kong, argued that Resnik, in his justification of the HIV trial, neglected to consider the broader issues of conducting clinical trials in the developing world. "In most of the developing countries, the neonatal morbidity is closely linked to the morbidity patterns of mothers. In simple terms, if an HIV-infected mother dies due to lack of treatment, the neonate born HIV negative will also eventually die, negating the benefits of the short-term AZT trial" (Thomas 1998: 324-325). Proponents also argued that it "would be a paternalistic imposition" (Petryna 2005: 187) for the U.S. to determine the kind of research design for parts of the world that are suffering from a major health crisis.

The debate about using a placebo instead of the known treatment—that remains unresolved to this day—led to the fifth revision of the Declaration of Helsinki in the year 2000 with significant changes made to paragraphs 29 and 30 of the Declaration. The changes essentially attempted to discourage researchers from the use of placebo when a known treatment exists stated that it is unethical to compare a new treatment only with a placebo and not with the known treatment (Vastag 2000) and also ensured access to care for trial subjects after the trial is over.

The revised paragraph 29 of the Declaration of Helsinki stated: "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", followed by paragraph 30 which states that "At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study" (WMA 2004 cited in Wolinsky 2006: 670). The issue of access to care after the trial was addressed for the first time in paragraph 30 of the Declaration. Paragraphs 29 of the 2000 revision faced great resistance, with critics like Robert Temple of the Centre for Drug Evaluation and Research of the FDA, arguing that only a placebo-controlled trial could actually prove efficacy and produce high quality scientific data (Petryna 2005). Paragraph 30 of the Declaration was also resisted, particularly by drug companies who would have to bear the costs of supplying drugs after the research was completed (Vastag 2000).

In response to the opposition to the placebo related statement in its fifth revision and the confusion it caused in the research community, the Declaration of Helsinki reiterated its position on the need for careful consideration in the use of placebo by issuing a clarification in 2002 and also making an addition to paragraph 29:

> The WMA is concerned that paragraph 29 of the revised Declaration of Helsinki (October 2000) has led to diverse interpretations and possible confusion. It hereby 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, under the following circumstances:

- 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;
Or,
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk or irreversible harm (WMA Declaration of Helsinki 2000 cited in CIOMS 2002).

The modification led to more contention. Critics argued that it "collides head on with the statement of paragraph 29 and is dangerously vague, permitting interpretations which could result in evident ethical infractions, where the billion dollar interests of the pharmaceutical industry manage to prevail, that is, in developing countries" (Marques 2002:975). According to physician Roni Marques, "it is frightening" that the use of a placebo and denial of a known effective treatment to trial subjects continues to be justified (Marques 2002:975). Unhappy with the 2000 revision, the FDA decided to adhere to older versions of the Declaration of Helsinki even though countries—particularly developing countries that are witnessing an increase in the numbers of clinical trials—are obliged to adhere to the tenets of the Declaration to obtain FDA approval (*Nature* 2008). Instead, Temple indicated a preference for using the International Conference on Harmonization (ICH) Guidelines on placebo use, for the ICH indicates that the decision on whether to use a placebo arm or not in a trial is best left to the judgment of patients, the investigator and the ethics committee or institutional review board (Petryna 2005). "Temple's invalidation of an active control trial" as opposed to no treatment or placebo, Petryna argues, emphasizes the importance of a treatment naïve subject, "precisely because they are often poor, without a treatment history, and without treatment, the treatment naïve are the more foolproof and valuable research subjects!" (Petryna 2005:188). Others argue that by rejecting the Declaration, the FDA "risks sending a message that ethical considerations are expendable when research subjects live half a world away" (*Nature* 2008:428).

The pharmaceutical industry, which also opposed the fifth revision of the Declaration of Helsinki, had by then begun their search for human subjects in the developing world. They now found ways to work around the ambiguous Helsinki statement, "best current" treatment, which could potentially be interpreted to mean the best local equivalent of treatment that could be far inferior to the acceptable standard of care for

patients in the developed world. Ethics therefore becomes a "workable document" says Petryna (Petryna 2005:189), who argues that poor public health conditions in the developing world could legitimize an ideology of "ethical variability" (Petryna 2005: 184) in the application of ethical standards in clinical trials conducted in less wealthy nations.

Although, unresolved issues remained, the Declaration of Helsinki stayed as a fundamental guideline for human subject protection in clinical research, with its principles being adopted by the majority of institutions conducting research on human beings (Levine 1988).

3. U.S. federal policies for ethical review and the protection of human research subjects

The U.S. that has among the largest number of clinical trial sites in the world (Thiers, Sinskey and Berndt 2008) was one of the first countries to formalize the importance of ethical review of clinical research in national policy. Since the 1960s, U.S. government regulations have gradually introduced the requirement for all federally funded research to undergo ethical review. The Surgeon General of the United States Public Health Service (USPHS) declared the first federal policy for the protection of research subjects in the year 1966. The policy stated that all grantees of the USPHS will not be given permission to undertake clinical research unless the investigator's application had reviewed for the methods used to obtain informed consent, the risks and benefits of research and the overall rights and welfare of research subjects (Levine 1988).

The 1966 policy statement was the outcome of immense pressure on the U.S. Congress to initiate legislation for human subject protection in the aftermath of wide scale revelations about human subject abuse in clinical research. One of the most influential pieces of writing on unethical human experimentation that forced the state to recognize the issue was an article published by Henry K. Beecher, in the *New England Journal of Medicine*, in 1966 citing 22 examples of unethical studies conducted on the American people. Beecher provided evidence of "the unfortunate separation between the interests of science and the interests of the patient" and added "that thoughtlessness and carelessness, not a wilful disregard of the patient's rights, account for most of the cases encountered (Beecher 1966:368). Beecher argues in his

paper that had the subjects been aware of the risks involved in the experiments they would not have consented to the experiments (Beecher 1966; Schneider No Date [n.d.])

In 1974, the U.S. regulations for human subject protection were codified by the Department of Health, Education and Welfare—now known as the Department of Health and Human Services or HHS—as 45 CFR 46, Subpart A and in the year 1991, Subpart A of 45 CFR 46 was adopted by 16 federal agencies and came to be known thereafter as the Common Rule (Williams 2005). Today the Common Rule applies to 18 federal agencies and departments. It requires that all human subject research, funded by any one of the federal agencies, should be reviewed by an Institutional Review Board (IRB)–from here on referred to as the Institutional Ethics Committee or IEC. Guided by the fundamentals of the Nuremberg Code, the Common Rule ensures human subject protection through three main requirements: review of research by an IEC; informed consent of human subjects and assurance from the institution of regulatory compliance. In addition, the Common Rule requires the IEC to ensure that the risks of research are minimized, that risks are reasonable in relation to potential benefits, the equitable selection of trial subjects and other aspects of protecting subjects in research (Williams 2005). Regarding the composition of IECs, the Common Rule requires that all IECs have at least five members from multi-disciplinary backgrounds, at least one member whose primary concern is in scientific areas, at least one member whose primary concern is in non-scientific areas and at least one member who is not affiliated to the institution. The Common Rule also describes criteria for protocol reviews and specifies the kinds of reviews (Williams 2005). Today, several research projects in the U.S. that are not federally funded also follow the Common Rule for research using human subjects even though it is not a legal requirement (Williams 2005).

In addition to the Common Rule, the other federal agency that requires review by an ethics committee is the FDA (Williams 2005). In 1981, the FDA published regulations on the functional and operational aspects of IRBs in reviewing clinical trials. The agency is directly involved with review of research protocols, can override a decision made by an ethics committee and monitors ethics committees through an inspection process, (HHS, Office of Inspector General 1998).

4. National Research Act, 1974

When the Tuskegee trial became public knowledge in the 1970s, the U.S. Congress consolidated its legislation for protecting the rights of research subjects in the National Research Act of 1974. The National Research Act led to the establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research—from here on known as the National Commission. The 1970s and 1980s was a time when the American public was increasingly sceptical of the medical profession. Faith in medical science was being replaced by suspicion (Fleetwood *et al* 1989). The Tuskegee experiment "catalyzed the new governance of research conduct as well as the rise of modern bioethics" (Petryna 2009:63).

Prior to the revision of the Declaration of Helsinki in 1975 that stated the need for an ethics committee, the international ethical guidelines for human subject research at the time, the Nuremberg Code and the first Declaration of Helsinki, placed the responsibility of protecting human subjects in a clinical trial entirely on the physician-investigator (Levine 1988). The U.S. National Commission explicitly stated that investigators should not be the only party responsible for upholding ethical standards in research and for ensuring a balance between the interests of society on one hand with those of the individual subject on the other. It iterated the importance of ethics committees comprising individuals who are independent of research to share the burden with investigators who are constantly torn between the pursuit of knowledge while simultaneously protecting the trial subject (Levine 1988).

- **The Belmont Report**

In 1979, the National Commission prepared a report that became the defining code for ethics committees across the world. The report titled Ethical Principles and Guidelines for the Protection of Human Subjects of Research is also known as the Belmont Report, from the Belmont Conference Centre where the Commission met to deliberate on issues of human subject protection (U.S. Department of Health, Education and Welfare 1979). The essence of the Belmont Report is the identification of three basic ethical principles: Respect for Persons, Beneficence and Justice. These ethical principles that today constitute the fundamentals of ethical research involving human subjects are the guiding principles for the human subject protection regulations of the U.S. Department of Health and Human Services (Petryna 2009).

Robert Levine, Professor of Medicine at Yale University, defines the three fundamental ethical principles as those principles that form the "ultimate foundation for any second-order principles, rules, and norms" and those that are not "derived from any other statement of ethical values" (Levine 1988:15). It is the responsibility of the ethics committee to apply these ethical norms, "which in turn represent requirements (e.g., for informed consent)" that derive from the three fundamental principles (Levine 1988: 12).

The principle, Respect for Persons, stresses the importance of recognizing individuals as independent and autonomous beings with the ability to make their own decisions about participating in research. Respecting a person's autonomy, as defined in the Belmont Report, means that we must leave individuals "alone, even to the point of allowing them to choose activities that might be harmful" (Levine 1988:15). The National Commission also recognized that not all individuals are "capable of self-determination" (Levine1988:16) or have the ability to make decisions for themselves, such as children, prisoners, and those with mental disabilities. These individuals, with reduced autonomy, must therefore be entitled to protection from the harms of research (Levine 1988).

The principle, Respect for Persons is to be achieved by the procedure of informed consent. The consent process comprises three elements: firstly, complete and relevant information about the proposed research, such as its purpose and the risks and benefits involved, should be given to the potential trial subject so that an informed decision can be made to either participate in the research or to deny consent; secondly, the information provided should be clearly understood by the individual; and thirdly, the element of volunteerism must be present in the process of consenting and individual decisions should be free of coercion or undue influence. The Belmont Report adds that the application of individual autonomy can be problematic in some situations. For example, prison populations might participate in research due to coercive conditions in prisons but at the same time prisoners should not be denied the opportunity to benefit from participation in medical research. The researcher is therefore presented with the ethical dilemma of whether to respect the prisoner's decision to participate or to protect the prisoner from a potentially exploitative situation (U.S. Department of Health, Education and Welfare 1979).

The principle of Beneficence refers to the responsibility of protecting research subjects from harm and ensuring their welfare in the course of a clinical trial. The principle of Beneficence obliges the investigator to maximize benefit and minimize harm in research and gives rise to the ethical norm that requires the risk of research to be reasonable in relation to the benefit (Council of International Organizations of Medical Sciences 2002). The principle also obliges the investigator to acquire knowledge that will be beneficial to society at a later stage but advises that the interests of society should not override the interests of the individual and intentional harm should not be inflicted on the individual in order to produce benefits for society (Levine 1988). The application of the ethical principle of Beneficence is not always clear-cut particularly when research that uses children as research subjects indicates more than minimal risk and presents benefits that are not immediate to the children who participate (U.S. Department of Health, Education and Welfare 1979).

The principle of Justice implies the need for a fair distribution of the benefits and burdens of research among persons. Research is defined as unjust when only one kind of population will benefit from the research and only one kind of population will suffer the burden of it. The principle of Justice in the Belmont Report refers to the obligation to prevent certain classes of people from disproportionately bearing the burden of research due to their economic, social or other vulnerabilities and ensuring that their selection to the research is relevant to and based on the actual problem under investigation. The principle of Justice, is thus, essentially referring to the understanding of distributive justice that requires "a fair sharing of burdens and benefits" of biomedical research (Levine 1988:17).

5. International Ethical Guidelines for Biomedical Research Involving Human Subjects-the Council of International Organizations of Medical Sciences

In 1982, the Council of International Organizations of Medical Sciences (CIOMS)[4], an International NGO, collaborated with the World Health Organization (WHO) to issue the Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects. In 1993, the proposed guidelines were extensively revised and formalized with the objective of providing guiding principles for the application

[4] The Joint United Nations Programme on HIV/AIDS provided substantial financial support to the development of the 2002 CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS 2002)

of the Declaration of Helsinki (CIOMS 2002) particularly for concerns that arise from multinational research undertaken in developing countries (Levine 1999). The Council made significant statements to ensure the prevention of exploitation of research subjects in the Third World. The CIOMS guidelines stated that any research sponsored by an agency from an industrialized country and conducted in the developing world must ensure that the research objectives are based on the health priorities and needs of the particular country. Moreover, the Guidelines also stated that the benefits of research should be "made reasonably available to the inhabitants of the host country. This then focuses multinational research on the needs of the country in which the research is carried out. No more conducting Phase I drug studies in Africa simply because it's less expensive and less vigorously regulated" (Levine 1999:175).

After 1993, CIOMS had to also consider the altered landscape of clinical trials that were increasingly becoming globalized and being conducted in low-resource countries. The emergence of HIV/AIDS and the high cost of AIDS treatment in poorer countries raised new ethical concerns. Updating the 1993 revision was complex as there were two camps on the ethics of clinical trial operations in the developing world. One group advocated for clinical interventions, that, although might be less effective than those used in the developed countries will also be affordable. Those opposing this view believe that trials in low-resource countries had the potential for exploitation. Guideline 11 of the CIOMS guidelines, on the choice of control in clinical trials, was redrafted in an attempt to accommodate opposing views on placebo use: those who argued that human subjects in developing countries should not be exposed to a placebo or no treatment when a known effective intervention exists and those who believe that placebo can be used even if a standard of care exists. It states: "As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo" (CIOMS 2002, Guideline 11:54). The term "best current" intervention used by the Declaration of Helsinki to denote the active comparator group of a trial is replaced by "established effective intervention" (CIOMS 2002, Guideline 11:54) by CIOMS. The CIOMS states, that, "in some cases an ethical review committee may determine that it is ethically acceptable to use an

established effective intervention as a comparator, even in cases where such an intervention is not considered the best current intervention" (CIOMS 2002: 13).

The CIOMS guidelines recognize the challenge in the ethics of international research of applying universal ethical principles in contexts characterised by multiple health systems and different standards of health care (CIOMS 2002:11). The Guidelines seek a compromise between the pluralist view, which contends that variations should be permissible in the application of ethical standards, and the ethical universalists who believe that ethical standards must be the same everywhere. The CIOMS guidelines state: "research involving human subjects must not violate any universally applicable ethical standards, but acknowledge that, in superficial aspects, the application of the ethical principles, e.g., in relation to individual autonomy and informed consent, needs to take into account of cultural values, while respecting absolutely the ethical standards" (CIOMS 2002:11).

Two of the eleven Guidelines of CIOMS updated in the year 2002 describe the role of the ethics committee with specific mention of ethical review of international research:

> All proposals to conduct research involving human subjects must be submitted for review of their scientific merit and ethical acceptability to one or more scientific review and ethical review committees (CIOMS 2002, Guideline 2: 24).
>
> An external sponsoring organization and individual investigators should submit the research protocol for ethical and scientific review in the country of the sponsoring organization, and the ethical standards applied should be no less stringent that they would be for research carried out in that country (CIOMS 2002, Guideline 3: 30)

6. World Health Organization (WHO) Operational Guidelines for Ethics Committees that Review Biomedical Research, 2000

The WHO guidelines for ethics committees were developed in the year 2000. Their objective was closely examining existing international guidelines for ethics committees, in order to achieve an "international standard for ensuring quality in ethical review" (WHO 2000:1). The Guidelines are written for "national and local bodies in developing, evaluating, and progressively refining standard operating procedures for the ethical review of biomedical research" (WHO 2000:1). The guidelines describe the role of ethics committees, the elements of an ethical review, the decision-making as well as the decision communicating process, composition and

membership of ethics committees and other procedural aspects of the role and functioning of ethics committees. The WHO is currently in the process of updating its guidelines for ethics committees in order to clearly define the benchmarks that should be adopted by ethics committees across the world. The draft identifies different kinds of standards: standards for the institution that appoints the ethics committee, standards for policy for sufficient funds and human resources to run the ethics committee and standards for the secretariat of the committee, standards to ensure the independence in ethics committee functioning and decision making and importantly standards and guidance for ethics committee members in the course of protocol review.

7. Clinical Trials Directive of the European Parliament and the Council of the European Union, 2001[5]

The Clinical Trials Directive was issued in the year 2001 with the objective of harmonizing clinical research and creating uniformity in clinical trial standards across Europe. The protection of patients in research was stated as the key purpose underlying the clinical trials Directive. The Directive explicitly states the integral role of the ethics committee is approving clinical research:

> A clinical trial may be initiated only if the Ethics Committee and/or the competent authority comes 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 (Official Journal of the European Communities 2001, Article 3:37)

The Clinical Trials Directive lists the kind of information that is to be reviewed by an ethics committee such as the relevance of the clinical trial, the investigators brochure that should contain pre-clinical and clinical data of the product under study and the protocol that should include the research objectives, design and methodology of the study. The Directive gives an ethics committee a minimum of sixty days to respond to a research application.

It was mandatory for all member states of the European Union to adopt the Clinical Trials Directive into their domestic legislation. However, there has been resistance to

[5] The full title of the Directive is: The European Parliament and the Council of the European Union (2001) 'Directive 2001/20/EC of the European parliament and of the council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use'. It is shortened in this document to 'Clinical Trials Directive' or Directive.

enforcing the Directive primarily due to its lack of consideration of problems faced by non-commercial academic research. Moreover, the Directive makes no distinction between regulations to be followed by commercial and non-commercial research (Hartmann and Hartmann-Vareilles 2006). Alyn H. Morice from the School of Medicine, in Castle Hill Hospital in the U.K., believes that the Clinical Trials Directive signals "the death of academic trials" and the "one size fits all policy" (Morice 2003: 1568) will make it difficult for student researchers to continue their work. Other critics of the Directive such as independent investigators and non-commercial research agencies fear that they will not be able to afford the additional resources such as staff and infrastructure required in order to meet the regulatory demands of the Directive (*The Lancet* 2003; Hartmann and Hartmann-Vareilles 2006).

8. Ethical review in the United Kingdom and the Impact of the European Union's Clinical Trials Directive

In 1964, the Royal College of Physicians in the United Kingdom (U.K.) recommended that all research using human subjects should undergo ethical review. The publication of 'The Human Guinea Pig' by M.H Pappworth in 1967 was a major catalyst for change in the ethics and regulation of human research in the 1970s (Elliott 2008). Guidelines for the functioning of ethics committees appeared later in the 1980s but it was only in 1991 that the Department of Health formalized ethical guidelines and made the formation of a local research ethics committee, an essential requirement for every health authority in the U.K. (Alberti 1995; Kerrison and Pollock 2004). The ethics committees in the U.K. that were either attached to a district or an individual institution functioned independently of the hospital, area or government. With reforms instituted in 2004, the ethics committees in the U.K. lost their relative autonomy and were required to function under the rules of the European Union Clinical Trials Directive. While the old system of self regulation had is strengths such as: personal communication with investigators which helped in avoiding misunderstandings, the discretion of the chair in initial protocol review, the advantage of a local research committee because of its familiarity with the local research community, there were also drawbacks that included: insufficient resources, lack of coordination between several ethics committees and the lack of transparency and public accountability. In spite of the drawbacks however "the move from self

regulation to direct political control of research ethics is a cause of concern in the ethics community" (Kerrison and Pollock 2004: 488). For example, the imposition of rules such as the requirement of a complete ethics review within sixty days, or permission to send the protocol back to the investigator only once, raised concerns about the quality of decision making and the capacity and time to negotiate with the investigator (Kerrison and Pollock 2004).

III. Global Studies on Institutional Ethics Committees

In the 1980s and 1990s, not long after the need for ethical review of clinical research was formalized in policy and international ethical guidelines were developed, studies IECs were initiated across the developed world. Concerns about the performance and effectiveness of ethics committees arose in the context of revelations of human subject abuse in biomedical research, with some assuming a scandalous nature and generating great media interest (Ashcroft and Pfeffer 2001). Literature on the subject from this period and in later years indicates that there was a debate and critical inquiry into the role of ethics committees. Questions were raised such as: what really is the role of an ethics committee in regulating medical research? How well are they performing their role as protectors of the welfare of research subjects? What are the operational limitations of these ethical review boards? What are the measures that can be adopted to strengthen the system of human subject protection?

Among the first known surveys done on ethics committees was the one conducted by B. Barber *et al*, in the U.S. in the year 1969. The survey interviewed one individual from each of the three hundred selected IECs, seventy percent of which had existed before the 1966 U.S. policy requirement for ethical review. The survey found that only a few committees had sent back protocols to be modified with 34 percent having never rejected a project or asked for changes (Barber *et al* 1969 cited in the National Research Council 2003). Another study on institutional ethics committees was conducted in 1978 for the National Commission. The study sample included over eight hundred IEC members. The study found that ethics committees were vastly different in their size, numbers of proposals reviewed per year, hours of work per year and in the number of meetings attended. There were also differences in committee procedures: in only half the committees could investigators make an appeal regarding a decision made by the committee; one-fourth had investigators attend the meetings

when their projects were being reviewed; two-thirds required a simple majority vote for project approval, while one-fourth needed a unanimous decision (Gray, Cooke and Tannenbaum 1978 cited in the National Research Council 2003).

In 1995, Raymond G. De Vries from the Centre of Bioethics, University of Minnesota and Carl P. Frosberg from Boston College in Massachusetts, surveyed a random sample of 89, of the 892 IECs registered with the Office of Human Research Protection (OHRP) in the U.S. According to the researchers few attempts had been made to understand the operational aspects of the committees and information about their members. The survey therefore attempted to look into the "black box" of IECs (De Vries and Forsberg 2002:200) so that reform in the systems of human subject protection could be initiated. The findings of the survey were analyzed in 2001. It was found that all IECs of the study were following federal regulations relating to the appointment of at least one member whose concerns lie in the realm of the non-scientific and one member who is not affiliated with the concerned institution. The study also found, that the membership of the IECs leaned towards Whites, medical researchers and those connected with the institution. The study raised the issue of the lack of support—inadequate resources and dedicated staff—that resulted in insufficient review and monitoring by IECs, leading to the eventual closure of research programs in several institutions by the OHRP. Among the key conclusions of the study was that "public failures of science are not the simple result of evil scientists driven by greed or blind ambition. Rather they are a product of structural problems in the system of review created to protect human subjects" (De Vries and Frosberg 2002:213). The authors of the survey expressed the need for more studies to be conducted to understand how members interact and make decisions and the functioning of the review boards.

In 1998, the U.S. Office of Inspector General, of the HHS issued a report on its study of IEC performance in reviewing on-going research or protocols that had already been approved. The study found that the ethics committees had limited time for on-going review and rarely visited clinical trial sites to ensure ethical compliance by investigators in the field. Among the reasons stated for limited on-going review was large workload and cost constraints. Due to a lack of funds the study found that volunteer members of ethics committees are pressured by their institutions to focus

their time on lucrative clinical research projects rather than on ethical review. The study also found that ethics committee members spent disproportionate amounts of time on reviewing the structure and content of informed consent forms rather than on ensuring that the information is understood by the potential trial subject:

> Many IRBs strive to see that consent forms are as informative and clear as possible. But these efforts often run against the grain as the forms become longer and more complex, serving more as documents to protect the institutions and the sponsors rather than the human subjects (HHS, Office of Inspector General 1998).

Robert J. Levine described the inadequacies in the functioning of Institutional Ethics Committees in the U.S.:

> There is a sense of crisis in the country about the effectiveness of the nationwide system that protects the rights and welfare of human research subjects. Reports of problems appear on television or in newspapers almost weekly and focus attention on the system's centerpiece, the institutional review board (IRB). University hospitals' entire research programs have been suspended on grounds of inadequate IRB performance, and governmental systems have found that the IRB system is incapable of coping with its workload (Levine 2001:161).

In 1981, a survey was conducted in Wessex, in the U.K. on individual ethics committee members and other members of the medical profession to understand their perceptions about the role of ethics committees. The survey's findings included polarized views among medical members regarding the role of non-medical members: on the one hand the role of lay ethics committee members were perceived by medical members as a "purely window-dressing exercises serving little or no useful function" (Allen and Waters 1983:64). The medical members believed that the requirement for having lay committee members was to appease public sentiments because in reality non-medical members placed obstacles in the progress of science. On the other hand non-medical members were perceived as having an important role to play providing a balanced and objective view to the research and in sharing their expertise in non-medical fields. Forty-two percent of the respondents expressed the need for training in medical ethics. Regarding the important issue of monitoring, only 38 percent of the medical members were in favour of ethics committees monitoring the progress of the research as opposed to 86 percent of the non-medical members. The authors state that regarding the response of medical members to the issue of monitoring, "it is not clear

whether this lack of enthusiasm for monitoring relates to a feeling that the logistical problems of undertaking this would render it of little use or whether the medical members feel that researchers, having once had a project approved, should be allowed to proceed without further interference (Allen and Waters 1983:62). The authors of the survey also state that in the past 15 years since ethical reviews have been conducted in the U.K., very little work has been done to create a forum both in the public and among the medical fraternity to openly discuss the problems faced by committees (Allen and Waters 1983: 64).

In 1998, a survey of hospital ethics committee chairpersons was conducted in the state of Maryland in the U.S. to assess the competence of ethics committee members. The survey found that less than one-third of the committees had a formally trained bioethicist or philosopher and there was little institutional support provided to ethics committees (Hoffmann, Tarzian and O'Neil 2000).

Studies have also focused on ethics training for IEC members who are not affiliated to the institution and those with a non-medical/non-scientific background. For example, a study done in the year 2000, in the U.S. on 'The Roles and Experiences of Non-affiliated and Non-scientist Members of Institutional Review Boards' found that of the 32 lay members (from 11 of 20 randomly selected IECs) who participated in the study, 72 percent had been provided with documents such as federal regulations, guidelines and IEC instruction manuals without any training or guidance on how to use the documents. Only 22 percent of the lay members had been given any formal training. Almost all participants (94 percent) believed that their main task on the ethics committee was to make informed consent forms more comprehensible, with one member stating that lay members should not be asked to examine adverse event reports The study found that learning on the job or listening in on IEC meetings was an effective way of understanding scientific and ethical issues for non-affiliated/non-scientist committee members. Forty-seven percent of the participants experienced the lack of sufficient training in science and ethics. One member expressed difficulty in reviewing adverse event reports and stated that lay members should not be required to examine such technical information (Sengupta and Lo 2003).

Outcomes of research conducted on ethics committees have led researchers to suggest reforms to improve the quality of ethical review. Pauline Allen and W.E Waters, from

the University of Southampton, in the U.K., suggests the need to facilitate communication among ethics committees so that "frequently encountered problems" (Allan and Waters 1983: 64) can be shared and discussed with members who can learn from each other's experiences. Levine suggests the need to rethink the responsibilities entrusted to IEC members. He believes that the recommendation of a system of monetary rewards to members will not necessarily improve performance particularly in an academic medical centre where "money is not the most important coin of the academic realm" (Levine 2001:162). Levine argues that IEC members waste vast amounts of time focusing on periodic evaluations and adverse events reports. He states that some responsibilities of an IEC could be delegated to a central ethical review body especially with regard to multi-centre trials. Levine is of the opinion that an IEC's role should be realistic and reasonable. An efficient education system for IEC members with an accreditation system and method of certification for its members will help in IEC performance that is in tune with the capabilities of its members (Levine 2001). Based on their study findings, Sengupta and Lo, professors at American Universities, stated the need to formalize ethics training for new non-affiliated/non-medical members. They also recommend a mentoring programme for newly appointed ethics committee members that would require them to work closely with more experienced members on the committee while reviewing protocols. Continuing education in the form of conferences and workshops was also recommended by the study as it would be extremely beneficial to lay members of IRB, instilling in them a greater confidence with which to participate more actively in IRB meetings (Sengupta and Lo 2003). Joseph Millum from the National Institutes of Health and Jerry Menikoff from the Office of Human Research Protections, in the U.S., suggest the need to streamline ethical review. They argue that IECs underutilized provisions provided in the regulations that could help in the making of a more efficient ethics committee. For example, in the case of multi-centre trials where more than one institution is involved, the IECs end up duplicating their work because each IRB reviews the same protocol. The Common Rule, has a provision allowing for the option of a joint review in such cases but this provision is not commonly used due to fear of liability and IEC "reluctance to cede control" (Millum and Menikoff 2010:656)

Other debates on ethics committees centre on the broader and more fundamental issues of IEC role and functioning. In 2004, a paper published in the *Journal of Medical Ethics*, titled 'Research Ethics Committees and Paternalism', the authors, Edwards, Kirchin and Huxtable argue that research ethics committees should not be paternalistic in their role as regulators of medical research because research subjects are competent enough to make their own decisions about the risks and benefits of the research and the autonomy of research subjects must be respected. They believe that "ethics committees should concern themselves *only* with helping to ensure consent is genuine, and not with trying to stipulate what level of risk is reasonable or unreasonable" (Edwards, Kirchin and Huxtable 2004:89). The reasons the authors give is because ethics committees do not come into direct contact with research subjects and are therefore not in a position to assess a potential subject's beliefs and decision making abilities. According to Edwards, Kirchin and Huxtable, an ethics committee can only assume a paternalistic role, when financial inducements or "psychological manipulation" such as threats to withdraw certain privileges and other means are used to coerce individuals into participating in a trial (Edwards *et al* 2004:90). Their argument against ethics committees being "extensively paternalistic" (Edwards et al 2004: 91) was refuted in an article published a year later, also in the *Journal of Medical Ethics* by authors Garrad and Dawson from the Centre for Professional Ethics at Keele University in the U.K. While acknowledging differences of opinion regarding the role of ethics committees, Garrad and Dawson argue that emphasis of autonomy must be dealt with caution as it can overlook problems that stem from the subject's lack of understanding of trial designs—for example use of randomization in a controlled clinical trial, that could pose potential risks—even though they might be competent enough to give their consent. Autonomy therefore should be balanced with the other ethical principles and in some cases be "overridden" by the other "moral considerations" such as "beneficence" and "non-maleficence" (Garrad and Dawson 2005: 420).

Lars Noah, a professor of law in the U.S., asks why IECs should be criticized for their "lack of transparency" when federal regulations only require " 'another gut check' " (Noah 2004: 272) from the ethics committees. Noah argues that the ethics committee represents "only one of several layers of protection against unethical" research on human subjects with other federal agencies like the FDA and the National Institutes of

Health (NIH) closely scrutinizing biomedical research protocols for ethical compliance, risk-benefit assessments, scientific integrity and appropriate informed consent. Even editors of biomedical journals are relied upon for their increasing role in the regulation of investigators of clinical research. Noah suggests that instead of having unrealistic expectations of IECs in the U.S. it would be better to have government agencies like the FDA and the NIH take on some of the work of the already burdened IEC (Noah 2004).

IV. Ethical Violations in India's Global Clinical Trial and the Development of Ethical Regulation

1. Unethical clinical trials in India

The literature on ethical violations in clinical trials in the country mostly discusses violations that took place from the 1990s onwards when India began its process of economic liberalization. Reporting ethical violations in clinical trials sponsored by multinational drug companies increased in the following decade when India initiated landmark legislations that facilitated the global pharmaceutical industry in conducting its clinical research operations in the country. From the available literature—mainstream media reports, articles published in the *Indian Journal of Medical Ethics*, research conducted by the Centre for Studies in Ethics and Rights and investigations conducted by women's organizations and individuals—we know that ethical violations have taken place in clinical trials using unsuspecting subjects with limited agency.

Nundy and Gulhati liken the conducting of clinical trials in India by foreign pharmaceutical companies, to a "new colonialism" (Nundy and Gulhati 2005:1633). According to Nundy and Gulhati, India does not have the infrastructure and trained manpower to conduct clinical trials. The DCGI is understaffed and also lacks the necessary expertise to review clinical trial protocols. Moreover, there are only about two hundred investigators trained in GCP guidelines, a handful of pathology laboratories that comply with ethical practice and only about half of the larger hospitals have institutional ethics committees who also lack the expertise to provide adequate ethical review of research. Given the inadequate clinical trial infrastructure, lack of human resource capacity and ineffective regulatory authority, Nundy and Gulhati state that illegal and unethical trials are a major concern for India. Kaushik

Sunder Rajan, while agreeing with Nundy and Gulhati's concern for unethical experimentation in India, adds that the "clinical-research landscape in India cannot be reduced to the neo-colonial exploitation of the local population...by rapacious multinational interests" (Sunder Rajan 2007:75). Sunder Rajan argues that even if clinical trials conducted in India "adhered to the letter of the law and spirit of ethical codes", the underlying structure of the global clinical trial dynamic in India "would remain one of exploitation" (Sunder Rajan 2007: 67). Sunder Rajan argues that the basis of unethical practices of clinical trials in India is not simply one of non-compliance to a set of rules and regulations but the result of a "network of economic and social relations that the international health industry has established on a global scale" (Sunder Rajan 2007: 67).

The discussion in chapter one on the collusion of interests of the main actors in a clinical trial, particularly the clinical trial industry and the state, in establishing India as a global trial site, is laid bare in the following examples of unethical clinical trials in India. Both Sunder Rajan's argument for the need of a more nuanced approach to understanding the unequal context of clinical trials in India and Nundy and Gulhati's argument of an inefficient regulatory and monitoring apparatus for clinical trials as being one of the reasons for unethical trials in the country hold true in the following examples of unethical clinical trials in India.

- **Quinacrine sterilization trials, 1980s-1990s**

In the 1980s, the use of quinacrine, an anti-malaria drug was promoted as a non-surgical and safe method of sterilization for women by two American researchers, Stephen D. Mumford and Dr. Elton Kessel. Mumford and Kessel's persistent advertising of quinacrine led to clinical trials being conducted across the developing world and resulted in the irreversible chemical sterilization of over 100,000 women (Freedman 1998: A1).

Studies on the long-term effects of quinacrine done in the U.S. suggest that quinacrine causes cells to mutate and according to WHO reports, 60 percent to 80 percent of known mutagens are carcinogens (Freedman 1998). In 1992, the ICMR had to terminate its quinacrine study due to a high failure rate (Rao 2001). In 1993, WHO announced that quinacrine should not be used for sterilization without sufficient laboratory research done on the drug. Due to uncertainty of the safety of the drug, the

U.S. also stopped sterilizations using quinacrine. In spite of these warnings of unproven quinacrine safety, thousands of women in India continued to be sterilized with quinarine. Several hundred doctors from both the public and private sectors and NGOs, including a doctor from the Lady Hardinge Medical College in New Delhi, extended their support to Kessel and Mumford in their promotion of quinacrine by conducting sterilization trials on women (Rao 2001).

The propaganda around sterilizing women in the Third World in the 1980s and 1990s must be understood in the context of the prevalent ideology of the time or rather the misconceived paranoia, that 'population explosion' in the third world—an outcome rather than cause of social and economic problems—would eventually lead to the entry of large numbers of Third World immigrants into the U.S. (Freedman 1998) posing "the gravest threat to the global environment (Rao 2001: 531).

Proponents of the use of quinacrine for sterilization believed that the method was beneficial to those populations where the use of contraception was limited and maternal mortality was high. This belief was based on the false assumption that maternal mortality is the result of unwanted pregnancies, when in fact, the majority of pregnancy related deaths in India are due to infectious diseases, under nutrition, anaemic deficiencies etc. Sterilization with quinacrine requires neither anaesthesia nor a trained individual to perform a surgery. While this is touted as a positive aspect of the method, "it is precisely these factors which endow the method with a high potential for abuse" (Rao 2001:528).

In 1998, the Supreme Court of India prohibited the use of quinacrine. The ban was the result of a Public Interest Litigation filed by the Department of Social Medicine and Community Health at the Jawaharlal Nehru University in New Delhi and the All India Democratic Women's Association (Rao 2001).

- **Drug trials at the Regional Cancer Centre, Thiruvananthapuram, Kerala, 2000**

In the year 2000, two new anti-cancer compounds M4N and G4N that had been declared unsafe by the U.S. FDA in the 1990s were tested on 26 oral cancer patients at the Regional Cancer Centre (RCC) in Thiruvananthapuram in Kerala. During the trial conducted by a researcher from the Johns Hopkins University (JHU) in the U.S., two patients died. Subsequent reports about the trial suggested that the trial subjects,

who were cancer patients in need of treatment, were not given adequate information about the risks and benefits of the experiment (Seethi 2001; Krishnakumar 2005). The trial was conducted without DCGI and ethics committee approvals and it was apparent that the American researcher selected India as the clinical trial site in order to circumvent the FDAs stringent regulations for testing new drugs.

Although JHU attempted to distance itself from the trial investigator and the RCC, its own internal inquiry found that the investigator had not received permission from an IEC and adequate animal testing had not been done. It is also alleged that while the controversy at the RCC had prevented the researcher from continuing the trial, a post-trial company, BioCure Medicals, based in Singapore and associated with the RCC trial's investigator from JHU, used the data derived from the unethical RCC trial to conduct trials in the U.S. with a license from JHU (Krishnakumar 2005).

- **Letrozole trials, 2003**

The drug Letrozole, internationally approved for the treatment of breast cancer in post menopausal women and not approved for any other use in any country, was tested in clinical trials in India in the year 2003, for its use as an anti fertility drug. The clinical trials, said to be sponsored by an Indian drug company, Sun Pharmaceuticals, were conducted in nine or more sites in various parts of India and enrolled over 400 women to test if Letrozole induces ovulation (Patranobis 2003). The women were not informed that they were participating in a clinical trial, informed consent was not taken from the trial subjects and permissions were not granted by the DCGI to conduct the trials (Nundy and Gulhati 2005).

Letrozole, which, is contraindicated in pre-menopausal women, is associated with foetal and genetic defects as well as stroke, paralysis, and pain in the joints (Patranobis 2003; Gulhati 2010). The drug sold in India under different brand names such as Letroz or Letoval, continues to be administered to infertile women in the country. A multi-disciplinary committee under a special director general of health services that was formed to make a decision about the potential banning of the drug for infertility treatment (Sinha 2011) stated that it will not ban Letrozole for infertility treatment. Instead, ICMR has been asked to conduct Phase IV trials over a period of two years to generate data to find evidence if the drug causes genetic and physical deformities in infants born through In Vitro Fertilization. Letrozole currently has a

market of rupees 37 crores in India and is growing at an annual rate of 35 percent (Sinha 2011).

- **Pneumococcal vaccine trials, 2007**

In 2007, the domestic unit of the U.S. drug company Wyeth Inc. conducted a paediatric Phase III trial at St. Johns National Academy of Health Sciences in Bangalore to test a pneumococcal vaccine. The trial that was conducted on 350 infants between 42 and 72 days old (Silverman 2008) was suspended by the DCGI in the year 2008 due to the death of an infant. The Indian trial was one of several global clinical trials to test the safety and effectiveness of the pneumococcal conjugate vaccine that is meant to prevent an infant from thirteen strains of bacteria compared to Wyeth's older vaccine, Prevnar that prevents seven strains (Silverman 2008).

Wyeth Inc. had been given permission by the DCGI to test the vaccine on healthy babies; however, the infant who died was enrolled in the trial in spite of a pre-existing cardiac disorder. Although, Wyeth had contracted a CRO, GVK Biosciences, to actually run the trial, it is the sponsor who should have been held legally responsible for the violation. In addition, in case of a violation the investigator of the trial must also be held liable for negligence and DCGI should also be accountable for not carrying out an inspection of the trial site (Silverman 2008).

According to Gulhati, the composition of the IEC of St. Johns National Academy of Health Sciences was unlawful because the chairperson of the ethics committee belonged to the same institution—a clear violation of the rules that require institutional ethics committees to select chairpersons from outside the institution (Personal interview with C.M. Gulhati on 4.3.2011) in order to ensure independence of the IEC in its decision making process.

The trial sponsored by Wyeth Inc. that violated ethical guidelines, clearly illustrates disregard for trial subject safety by both the multinational companies and local CROs. It also indicates a non-existent redressal mechanism for vulnerable subjects in case of trial-related death or injury and the lack of legal requirement for either the sponsor or the CRO to provide compensation in case of a trial-related death or injury.

- **Trials at the Bhopal Memorial Hospital and Research Centre, 2004- 2008**

Between 2004 and 2008 over 160 patients of the Bhopal Memorial Hospital and Research Centre (BMHRC) were made subjects of clinical trials that tested drugs and

New Chemical Entities. The trial subjects who were being treated at the BMHRC were unaware that they were being used in drug trials that carried on for several years. Ten subjects died in the course of the trials and no compensation was paid to the families (Gulhati 2010).

Over 80 percent of patients at this Hospital are victims of the Bhopal gas tragedy, suffering from serious health problems, and it is for their treatment that the BMHRC was established. The trials clearly violated ethical guidelines that prohibit conducting trials on people with reduced autonomy.

Clinical trials at the BMHRC were conducted for at least seven types of drugs developed by multinational pharmaceutical companies: telavancin patented by Theravance Inc., tigecycline by Wyeth, prasugrel and fondaparinux by GlaxoSmithKline (GSK) and fixed dose combinations of cefoperazone with sulbactum sold by Pfizer in India. One of the trials sponsored by Theravance Inc. of the U.S. and conducted with the services of the CRO, Quintiles, tested Telavancin, an antibiotic, which is also sold under the brand name vibativ. The Theravance trial was approved by the DCGI in the year 2006. However, Theravance got marketing approval for the drug Telavancin in the U.S. only in the year 2009 making the drug an untested New Chemical Entity when it was used on subjects at the BMHRC, therefore exposing extremely vulnerable and sick individuals to greater risks. Eight patients were recruited for the Theravance trial and in the course of a year, there were three deaths. The DCGI and IEC approving such risky trials is a question that remains unanswered. An article in the *Times of India* in the month of February, 2011, titled 'Bhopal gas victims now turn guinea pigs' reported that only one of the seven clinical trials held at BMHRC was inspected by the DCGI. This information only became public knowledge though an application filed under the Right to Information Act (RTI). The article also states that the Hospital earned over one crore Rupees as revenue from the clinical trials (Varma 2011).

- **TIDE (Thiazolidinedione Intervention with Vitamin D Evaluation) Trials, 2010**

In 2007, data on an anti-diabetic drug, Rosiglitazone (Avandia), revealed that the drug was associated with a 43 percent increase in the risk of myocardial infarction (Shah *et al* 2010) compared to a competitor drug, Pioglitazone (Actos), made by Akeda. A

report in the *News and Observer* in 2010 (Harris 2010) stated that the pharmaceutical company GSK, the innovator of Rosiglitazone, had covertly initiated investigations to research whether its own drug Avandia was better than Actos. A positive result for Avandia was crucial for GSK who was struggling with the production of new products. When the investigation about Avendia revealed negative information, GSK spent several years covering up the data instead of publishing it. In the year 2007, when data about heart risks posed by Avendia were made public (Harris 2010), the FDA required GSK to conduct a large scale trial to compare the cardiovascular risks between the two rival drugs in order to confirm the recently revealed global data (Gulhati 2010). The drug company began the multi-centre trial—also known as the TIDE or Thiazolidinedione Intervention with Vitamin D Evaluation trial—in the years 2009-2010, recruiting 16,000 patients from trial sites in countries like India, Columbia, Pakistan and Latvia and also the U.S. (Strickler 2010).

This Phase IV, post marketing trial, with inherent risks and limited relevance to India was still given approval by India's clinical trial regulatory body. Nineteen trial sites that were approved in the year 2010 and run by Quintiles, one of India's largest CROs were eventually suspended in the same year on grounds of unethical practice as a result of pressure put on the Ministry of Health and Family Welfare by organizations such as the All India Drug Action Network calling for urgent suspension of the TIDE trial. The suspension of the TIDE trial in India did not affect global operations that continued in 300 locations across the world (Strickler 2010).

- **Human Papilloma Virus (HPV) vaccine trials, 2009-2010**

In 2009, Phase IV clinical trials to test two vaccines for the prevention of HPV—the primary cause of cervical cancer in women—were conducted in the states of Andhra Pradesh and Gujarat by the U.S. based Non Governmental Organization, PATH (Programme for Appropriate Technology in Health) International in collaboration with ICMR and the respective state governments. More than 20,000 girls aged 10-14 years mostly from Scheduled Tribe communities in the states of Andhra Pradesh (Khammam district) and Gujarat (Vadodara district) were vaccinated with vaccines produced by two different multinational drug companies. The vaccine Gardasil manufactured by the India subsidiary of Merck & Co., Inc. of the U.S. was used in the trial in Andhra Pradesh and GlaxoSmithKlines Cervarix vaccine was used in Gujarat. Both vaccines were provided free of cost by the drug companies for the trial (Sama

2010). In the course of the trials seven girls died and many experienced side effects. Significant pressure was put on the Ministry of Health and Family Welfare (MoHFW) from women's groups, people's health movements, public health networks, child rights groups, human rights groups, medical professionals and members of parliament, leading to the suspension of the trials in 2010.

Thereafter the MoHFW constituted an Enquiry Committee to investigate the allegations that the clinical trials had violated ethical norms (Press Release on 9.5. 2011). The Committee submitted its final report in the year 2011. Three experts assisted the committee, two from the All India Institute of Medical Sciences (AIIMS) and one, who was an ICMR representative. The appointment of an ICMR employee as a part the trial's investigation indicates a clear conflict of interest, as ICMR was a partner agency in the trial.

The investigations revealed that the HPV trials violated ethical guidelines for human subject protection on multiple grounds.

The young trial subjects were made to believe that the vaccination was part of the national immunization programme being conducted under the auspices of the National Rural Health Mission. The public immunization programme has credibility among the local population and was used to gain acceptance among the people for a clinical trial conducted by a private agency (Karat 2011). The participants were also made to believe that there would be no major side effects and that they would be protected from cervical cancer for life. The vaccines are however believed to prevent only two among several hundred strains that cause cervical cancer and moreover, its efficacy beyond three and a half years has not yet been established (Personal Interview with C.M.Gulhati on 24.7. 2010).

Informed consent procedures for recruiting trial subjects, in this case minor girls, also violated India's ethical guidelines that clearly require either a parent or legal guardian to give proxy consent in the case of minor research subjects and consent procedures can only be waived in certain emergency situations or when confidentiality of trial participants is essential for their own protection (ICMR 2006). In the case of this trial, wardens, headmasters and teachers of the hostels and ashram schools where the children lived were asked to give proxy consent. The unethical process of consent was

facilitated by the Deputy District Medical and Health Officer of the Bhadrachalam in Andhra Pradesh who in a circular to the Project Officer of the area instructed "all the hostel wardens and Ashram schools to sign the consent forms on behalf of the Adolescent girls to have the vaccine, as contacting the parents will be difficult in agency area" (Rao 2009).

Another expert on the committee found negligence in the policy for reporting adverse events and the lack of a monitoring system after the vaccine had been administered. The expert was also critical of the delays in reporting the deaths of the young trial subjects and of the gaps in investigating the cause of the fatalities (Karat 2011).

The role of the two ethics committees appointed, one for each state, has also been questioned. The ethics committees held no meetings to review adverse event reports and assess the progress of the trial and only convened after negative reporting of the trial in the media (Karat 2011).

In a hasty cover up attempt, both ICMR and PATH have stated that the HPV trial was not a Phase IV clinical trial but a demonstration project and therefore did not have to comply with India's clinical trial regulations, such as the reporting of adverse events. Both the DCGI and an expert on the Enquiry Committee, found however, that the description of the project provided to the DCGI that describes the administration of a drug on human subjects with the objective of studying adverse effects is in fact one of the main objectives of a Phase IV clinical trial. Therefore the demonstration project, which is in fact a Phase IV trial, must follow the requirements of a clinical trial protocol (Karat 2011).

The final report of the Enquiry Committee that discussed the numerous ethical violations of the HPV trial failed to hold any of the concerned organizations—ICMR, Path, State Governments and ethics committees—accountable for not complying with ethical guidelines and regulations. Organizations such as Sama (Resource Group for Women and Health), Jan Swasthya Abhiyan, the Human Rights Law Network and individuals like Brinda Karat, Politburo member of the Communist Party of India (Marxist) and Member of Parliament, Amar Jesani, an independent researcher and editorial board member of the *Indian Journal of Medical Ethics*, C.M.Gulhati—all of whom have worked to expose the ethical violations of the HPV trial—demand that all

parties responsible for the ethical violations should be held accountable including the DCGI for approving the HPV trial and all data acquired from the trial should be disregarded. The demands also include preventing the vaccines' inclusion in the immunization programme due to prohibitive costs and focusing instead on screening facilities for cervical cancer that is one of the most effective ways to prevent the disease. The civil society groups also stated that the role of the ICMR and ethics committees as gatekeepers of the highest ethical standards of research in the country needs re-examination (Press Release on 9.5.2011).

- **Risperidone/Risperdal Trial, 2003**

Risperidone, an antipsychotic drug, was selected by the drug company Johnson & Johnson to test the drug's effectiveness for the treatment of acute manic or mixed episodes associated with bipolar disorder. The CRO Quintiles conducted the Risperidone trial in Gujarat. The period of the trial is not clear but sources reveal that it was probably around 2003 (Weyzig and Schipper 2008). The trial selected 290 psychiatric patients who had been hospitalized while suffering episodes of acute mania from four public and three private hospitals. Of the 290 trial subjects more than 210 were recruited from three government hospitals most probably because government hospital patients are among the worst off and the most vulnerable and are therefore easier to recruit (Srinivasan and Nikarge 2009).

The Risperidone trial was a placebo-controlled trial undertaken for a period of three weeks. The trial subjects or patients were taken off their regular medication for a period of about three days before being assigned to either the placebo arm or the Risperidone arm of the trial. The trial violated several ethical norms: patients were assigned to a placebo group and denied established antipsychotic treatment during the trial exposing them to unnecessary harm and therefore clearly violating the Declaration of Helsinki that advises great caution is the use of placebo when a known treatment exists. Informed consent was not obtained and patients were not adequately explained about their participation in a clinical trial. The trial subjects were also made to believe that their current medication was no longer available and therefore they were being taken off it (Weyzig and Schipper 2008; Srinivasan and Nikarge 2009).

Johnson & Johnson denied allegations regarding improper informed consent procedures used during the trial and also justified the use of the placebo by stating

that in a placebo controlled trial fewer subjects are exposed to a potentially ineffective treatment (Weyzig and Schipper 2008).

2. Guidelines for the protection of human research subjects and the development of ethical review

▪ Ethical Guidelines For Biomedical Research on Human Participants by ICMR

In India, the first officially established guidelines for ethical review of human subject research by an IEC are over thirty years old. The need for ethics review was first stated in a 1980 document—Policy Statement on Ethical Considerations involved in Research on Human Subjects—that was developed by the Central Ethics Committee of the ICMR, also known as the Justice H.R. Khanna Committee. The 1980 statement that was influenced by the principles of the Declaration of Helsinki (ICMR 2006) is not available in the public domain. It included guidelines on membership to the committees and ethical standards of review. It also stressed the need to give ethics committees enough independence to empower them to be effective regulatory bodies (ICMR 2006; Jesani 2009).

In 2001, ICMR issued the country's main document for the protection of human research subjects: Ethical Guidelines for Biomedical Research on Human Participants. The ICMR guidelines are derived primarily from the Declaration of Helsinki, the International Ethical Guidelines for Biomedical Research Involving Human Subjects established by CIOMS, the U.S. government's Common Rule and FDA regulations for IECs. These Guidelines later revised in 2006, are divided into two broad categories of general and specific guiding principles. The General Principles refer to the ethical norms of the ICMR, General Ethical Issues such as informed consent, selection of clinical trial subjects, compensation for participation and trial related injury and access to benefits after the trial. The Specific Principles apply to drug and vaccine clinical trials, epidemiological studies as well as guidelines for stem cell and genomic research. The Guidelines clearly state the need for all biomedical research to be evaluated by an Institutional Ethics Committee (or an independent ethics committees) and elaborate on the composition, role and functioning of Institutional Ethics Committees, the reviewing procedures, kinds of review and the documentation required for complete ethical review (ICMR 2006).

Since the ICMR guidelines like other international guidelines on biomedical research on human subjects is not a legally binding document, ethics committees do not have the authority to penalize or impose sanctions on those responsible for ethical violations committed in the course of a clinical trial. At the same time however, the ethics committee is a regulatory body authorised by Schedule Y (amended 2005) of India's Drugs and Cosmetics Rules that requires every clinical trial protocol in the country to be approved by the DCGI and an ethics committee. The ethics committee therefore has the authority to reject a trial on unethical grounds and it is not merely an advisory body in the clinical trial process (Jesani 2009).

- **Indian Good Clinical Practice (GCP) guidelines**

India's Central Drugs Standard Control Organisation (CDSCO), instituted its Guidelines for Good Clinical Practice (GCP) in order to harmonize the country's ethical guidelines and regulations with the guiding principles of the Declaration of Helsinki and with other international guidelines for human subject protection in clinical research: the WHO guidelines, U.S. federal regulations, the European GCP and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (Directorate General of Health Services, Ministry of Health and Family Welfare n.d.).

The Indian GCP is a comprehensive guiding document for investigators and sponsors of clinical trials and Institutional Ethics Committees. Among its main objectives is to create a uniform quality of clinical research throughout the country. The GCP, for example, provides an investigator with details of the essential elements of a research protocol, it describes the roles and obligations of a sponsor as well as provides guidelines for ethics committees. In addition to the ICMR guidelines, the Indian GCP also contains in its appendices relevant information and documents for conducting a clinical trial such as the Rules, the Declaration of Helsinki and information on the Investigator's Brochure, an essential document required for the process of approval of a clinical trial (Directorate General of Health Services, Ministry of Health and Family Welfare 2001).

3. Research on ethics committees in India

Research conducted on Institutional Ethics Committees in India is limited to a handful of studies. In the year 2002, ICMR conducted a WHO-sponsored survey of

Institutional Ethics Committees connected with clinical trials or research projects funded by the ICMR. The survey's objective was to fill gaps in available information about the functioning of IECs in the country (Mathur 2010) and to understand lapses in ethical review mechanisms in organisations conducting biomedical research in order to improve ethical standards of research in India. The ICMR intended to conduct its survey on 149 ICMR supported clinical trials or research projects across 71 institutions. However only 36 institutions responded to ICMR, in spite of all of them being recipients of ICMR support. While all 36 institutions claimed to have Institutional Ethics Committees only 23 had Standard Operating Procedures (SOP) in place; 24 of the committees had a separate scientific review committee and four had more than one ethics committee; only 14 had trained their members in bioethics, with no response from more than half the committees about their status on training. The survey also found that of the 149 projects, IEC clearance certificates were available for only 107 projects (ICMR 2006-2007; Kamath 2007; Jesani 2009).

There are very few studies in India that have attempted to assess the skills and competence of IEC members or to investigate if there are institutional policies and mechanisms in place to provide the necessary training to both affiliated and non-affiliated members of IECs. In 2005, a survey was conducted by the Clinical Trials Unit of the National AIDS Research Institute, in the city of Pune (Maharashtra), on the Profile and Role of the Members of Ethics Committees in Hospitals and Research organizations in the city. Fifty-two out of 87 ethics committee members participated in the study. Of the 52 members, 35 represented seven medical colleges and hospitals, 12 members represented three research organizations and five members represented two NGOs. Unlike the study done by ICMR, this survey interviewed the individual ethics committee members and not the institution. A self-administered questionnaire with multiple choice and open-ended questions covering topics such as working procedures, training in ethics and the decision making process, was given to each ethics committee member. The survey found that the ethics committee members usually occupied senior positions in their organizations, had several years of research experience and attendance at committee meetings was found to be significantly connected to higher qualifications and years of research experience. Almost half the participants were from medical backgrounds, 15 percent were social scientists and 33 percent fulfilled other membership criteria for the IEC such as legal and community

representatives. Less than half, 44 percent, of the participants had accurate knowledge of ethical principles and the majority, 79 percent, expressed the need for formal training in ethics (Brahme and Mehendale 2009). Authors of the survey strongly recommended the need for institutions to provide training in bioethics for ethics committee members. They also suggested the establishment of a network of ethics committees across the country so that members could have the opportunity to share ideas and consult other members on ethical issues (Brahme and Mehendale 2009).

In 2008, a study supported by the U.S. National Institutes of Health and ICMR was undertaken to understand the composition and functioning of Institutional Ethics Committees in ten public sector teaching hospitals. A semi-structured questionnaire was given to institutional heads and was completed by seven of the ten selected hospitals. The survey found that there was inadequate financial support for 43 percent of the ethics committees and only 25 percent of the committee members had training in bioethics. Regarding IEC composition, the survey found that the Chairperson of the IEC in one of the seven hospitals was also the head of the institution, while the Chairperson of four other IECs were affiliated to their institution (Singh 2009: 568). Some of the concerns raised by the IECs in this study were the lack of trained members, poor attendance at IEC meetings, inability to provide monetary incentives to IEC members and the need for an advisory body to advise members on complicated ethical problems (Singh 2009: 569).

Jesani states that there are several problems regarding the functioning of ethics committees in India. Firstly, there is little communication between the DCGI and the ethics committees even though the DCGI is entirely dependent on the ethics committee for regulating the ethical conduct of clinical trials in the country. Secondly, the DCGI pays little attention to the proper functioning of ethics committees; and the funding and running of the Institutional Ethics Committee is left to the institution that has a vested interest in conducting clinical trials. The independence of an Institutional Ethics Committee in ethical review is therefore questionable. Thirdly, there is no transparency in the functioning of ethics committees and neither is there an independent agency to assess the proper functioning of ethics committees. "The legal regulator [DCGI] has no idea how well the ethics regulator is working or whether it is working at all. Thus, the present decentralisation of clinical trial governance is a

highly irresponsible decentralisation of governance, exposing the legal regulator to the criticism of effectively abandoning its obligations to regulate" (Jesani 2009: 63).

Jesani questions why ethics committees "remain an enigma" (Jesani 2009:63) even 30 years after the first ethics committee was established in the country. There are no experiential accounts on ethics committees in the public domain and members of ethics committees are not willing to express the challenges and dilemmas they face in their work and there is little room for discussion to make ethical regulations more streamlined and effective (Jesani 2009). Gulhati expresses similar concerns about ethics committees in the country, stating that less than 40 ethics committees are adequate in their functioning and method of constitution (Gulhati cited in Jesani 2009). Gulhati also questions the autonomy of ethics committees particularly in corporate and drug company owned hospitals where members of these committees depend on the institution for their livelihood and the institution depends on clinical trials as a source of revenue (Personal interview with C.M. Gulhati on 4.3 2011). According to Gulhati, ethics committees cannot work as an effective regulatory body for several reasons. Firstly, the dependence of the hospital on the revenue generated from the clinical trial "dilutes" the role of an Institutional Ethics Committee. Institutional Ethics Committees can only play a role in the ethical conduct of research when there is no money involved, states Gulhati (Personal interview with C.M. Gulhati on 4.3.2011). In addition, Gulhati doubts the feasibility of an effective and independent IEC in the current scenario where drug companies are establishing hospitals and "doctors are at the beck and call of the hospital. If they disapprove [a protocol] they will be thrown out" (Personal interview with C.M. Gulhati on 4.3.2011).

Conclusion

The review of literature on the subject of ethics committees provides the conceptual framework for the study on: The Role of Institutional Ethics Committees in Clinical Trials: A Study of Selected Hospitals in New Delhi. It gives the reader a background on the history of the ethics committee and by citing several examples of unethical medical experiments particularly from the U.S. and India, the review emphasises the need for a regulatory agency to ensure the safety of the research subject. Studies conducted on IECs in India and abroad provide information on the role and

functioning of ethics committees and the range of problems faced by members of ethics committees. The studies and surveys conducted on ethics committees have helped the researcher in defining the research objectives of this study and in preparing the research tools. The absence of a substantial body of literature on ethics committees in India has been the impetus behind this study that seeks to fill the gaps in existing knowledge and more importantly investigate the challenges faced by members of institutional ethics committees. The next few pages of this chapter will discuss the research design, the research methodology and the research tools used for the study on Institutional Ethics Committees in New Delhi.

V. Research Design and Methodology

1. Research design

An exploratory study was conducted on members of Institutional Ethics Committees across selected hospitals in Delhi. The research design was exploratory in nature—using qualitative research methods—as there is limited literature about IEC members and on the role and functioning of ethics committees.

2. Study rationale

Research on Institutional Ethics Committees in India is limited to a handful of studies. Moreover, most of the research is in the form of surveys that do not provide any information on the nature of problems faced by IEC members. Ethics committees function in an ad hoc and arbitrary manner and there is no central registry for this regulatory body. Since the Rules for clinical trials were amended in 2005, the numbers of trials conducted in the country have increased and so have accounts of unethical clinical trials. These accounts of ethical violations that reveal the suffering of research subjects due to neglect by multinational drug companies, CROs or investigators bear evidence of the lapses in IEC functioning and the inability of these committees to effectively carry out their key responsibility of protecting the research subject. The system of human subject protection cannot be improved without an adequate understanding of how an ethics committee is run and who its members are. This study has endeavoured to fill the gaps in existing knowledge on the subject and has also attempted to contribute new knowledge by understanding the challenges faced by IEC members in the course of ethical review and exploring why ethics committee members are criticised for not carrying out their roles effectively.

3. Research questions

- Is the IEC in its existing form an adequate protective mechanism for trial subjects?
- Are IEC members carrying out their roles efficiently?
- Is there a need to rethink the regulatory structure in place for clinical trials?

4. Broad objectives

- To critically look at the positioning of the IEC as a key gatekeeper of ethical guidelines and principles in an increasingly global environment of clinical trial operations and ethical violations in clinical trials.

5. Specific objectives

- To understand the challenges and constraints faced by individual members of Institutional Ethics Committees in both public and private hospitals in Delhi.
- To understand the role and importance of ethics committees in India in the protection of trial participants.

6. Research methods

- **Study Sample**

Seventeen IEC members were interviewed across five hospitals in Delhi that were purposively selected by the researcher. Of the five hospitals: two are public institutions, two are private institutions and one is a trust hospital. To maintain anonymity, the hospitals are being referred to as Public Hospital A, Public Hospital B, Trust Hospital C, Private Hospital D and Private Hospital E. The hospitals were selected to represent both privately and publicly run institutions and also a trust managed hospital, to attempt an understanding of differences, if any, and similarities, between IECs of different types of hospitals.

One of the major criticisms made against ethics committees both in India and elsewhere is the "secrecy that surround them and their decision making" (Ashcroft and Pfeffer 2001: 1294). As there is no central or regional registry for IECs in India, any information on ethics committees in the public domain is left to the discretion of the institution. While the Clinical Trial Registry of India does have information on ethics committees on its website, the information is limited to a search for particular clinical trials and their associated ethics committees. Since there is no systematic

method of identifying the medical institutions in Delhi that have ethics committees and who the members are, the sample was purposively selected.

7. Sources of data collection

- **Primary sources of data**

a) Interviews with IEC members across five hospitals.

b) Clinical trial guidelines and regulations.

c) In addition to interviews with IEC members, findings are also based on:

- An interview with one clinical research manager from Private Hospital D.
- The Standard Operating Procedures (SOP) of IECs of Hospitals A, B and D.
- Other documents associated with IECs.
- Non-participant observation of an IEC meeting at Private Hospital D.
- The National Bioethics Conference 3, held in New Delhi from 17-20 November, 2010.
- Workshop titled 'Clinical Trial Regulations for India: Training for Regulatory Members in Industry and Ethics Committees' organized by the Indian Society for Clinical Research on 29 October, 2010.

d) Press conferences, seminars and personal interviews relevant to the subject on clinical trials and the drug industry.

- **Secondary sources of data**

Secondary sources of data included Indian journals, media reports and web-based searches of international peer reviewed journals.

8. Tools of data collection

- **The semi-structured interview**

A semi-structured interview schedule was used to interview IEC members representing five hospitals in Delhi. The interview guide was divided into two broad themes: the SOP of the IEC and the opinions and views of IEC members on a range of topics such as: ethics training for IEC members, ethical dilemmas while reviewing clinical trial protocols, IEC workload and challenges faced by individual IEC members.

9. Barriers to data collection

The researcher faced several challenges in identifying and accessing IEC members. Public Hospital A is the only institution that has detailed and current information on

the members of its IEC in the public domain, made available through the institution's website. The website of Public Hospital B has been under construction for the entire period of the study and therefore no information was available. The website of Trust Hospital C mentions an ethics committee but no further information is provided. The website of Private Hospital D has no information at all on its IEC. The website of Private Hospital E provides complete details about its IEC, however, the information is about members of the previous committee and not the current IEC.

The list of members of the IEC of Public Hospital B were provided in the ethics committee's SOP, but their contact information was not made available to the researcher. The Member Secretary of Public Hospital B informed the researcher not to approach the IEC members directly. The Member Secretary of Trust Hospital C provided no contact details or list of IEC members. The Member Secretary of Hospital C also made it clear to the researcher that no other IEC member could be contacted and only the Member Secretary would provide necessary information. As far as Private Hospital E is concerned, the non-affiliated member who the researcher was able to meet had signed a confidentiality agreement with the institution and therefore was not in a position to provide contact details of other members of the IEC.

Confirming appointments with some IEC members took several days to weeks and even months from the time of initial communication. Some IEC members, whose contact details were available, refused to meet the researcher despite multiple requests for a meeting and visits to their place of work.

The researcher perceived a sense of reservation in ethics committee members about sharing information on the workings of their committees. Further, since several members are departmental heads of large tertiary care hospitals with many institutional responsibilities, they had limited time or interest in the researcher. The researcher was given ten to fifteen minutes on average with each IEC member and therefore was unable to broach certain important ethical concerns in clinical trials that require in-depth discussions such as post-trial access, standard of care, subject recruitment and continuing review of approved research.

In addition to a general reluctance on the part of ethics committee members, some members were unsure of even basic information about their ethics committee. For

example, the Member Secretary of Trust Hospital C—whose main responsibility is to oversee the administration of the IEC—was unclear about the number of members on her committee.

Regarding access to the SOPs of each committee, the researcher obtained access to the SOP of the IEC of Public Hospital A from the website of the institution; the SOP of IECs of Hospital's B and D were provided by the Member Secretary and the clinical research department respectively. The SOP of the IEC of the Trust Hospital C was not made available to the researcher and it is not known if the IEC has constituted a SOP. The SOP of the Private Hospital E has been in the process of finalization for several years according to a non-affiliated member on the committee.

Although the researcher was fortunate to obtain access to one IEC meeting of Private Hospital D, all proceedings and minutes of IEC meetings are confidential and are not available in the public domain.

10. Limitations of the study

Although it would have been preferable to interview a larger number of IEC members, due to difficulty in identifying and accessing IEC members within a short period of time, the study sample is limited. The findings of the study cannot therefore be used to make generalizations of the entire population of IECs in institutions across Delhi and only represents the experiences and views of the IEC members who participated in the study and the workings of the specific IECs.

Chapter 3

The Role of an Institutional Ethics Committee

Introduction

The Indian Council of Medical Research describes three broad objectives for an IEC:

> 1. To protect the dignity, rights and well being of the potential research participants.
> 2. To ensure that universal ethical values and international scientific standards are expressed in terms of local community values and customs.
> 3. To assist in the development and the education of a research community responsive to local health care requirements (ICMR 2006: 9).

These goals are to be fulfilled through an ethics review of a clinical research proposal or protocol before a clinical trial has begun, during the trial and after it is over. The world over, institutional ethics committees have faced criticism for not carrying out their roles effectively. Reasons cited in the literature review for inadequate ethics committee performance include lack of ethics training, limited administrative resources, lack of transparency in member selection, lack of clarity in roles of non-affiliated/non-medical members, an overburden of protocols for review and an over-emphasis on procedural matters.

The first section of this chapter will attempt to describe some of these tasks. It will define the structure of an IEC and explain its essential mandate as stated in ethical guidelines and legislations. Although responsibilities of ethics committees are similar across countries as they are based on international guidelines, this chapter will refer particularly to the ICMR guidelines, the Indian GCP and the Rules. The second section of this chapter will look at the conceptual and practical difficulties in implementing some of the responsibilities ascribed to an IEC. Ethical guidelines and regulations abound in ambiguities and assessments such as risk and benefit, compensation for risk related injuries, post-trial access and undue inducement are not explained adequately or emphasized enough. Moreover, the lack of legislation on many aspects of clinical research leaves little opportunity for ethics committees to enforce adherence to ethical guidelines. The second section will attempt to discuss the range of issues debated around some of the essential tasks of an IEC. It will illustrate how the ground realities of conducting clinical trials especially in the developing world could create further barriers for IEC members in ensuring that the ethical

principles of justice, beneficence and autonomy will indeed be successfully applied.

I. The Responsibilities of an Ethics Committee

1. The IEC as an autonomous and voluntary body

Although an IEC is constituted by the head of an institution, it has been conceptualized as a voluntary and autonomous body with the authority to make decisions about a research protocol that are "free from any bias and influence" that could affect the objectivity of an ethical review process (Indian GCP: 23 n.d.). The regulations therefore require the Chairperson of an IEC to be selected from outside the institution to ensure that the IEC is "independent of the research team" (CIOMS 2002, Guideline 2:24). Members of IECs are professionals, each in their own right, who volunteer their time to attend ethics committee meetings. While members may receive some form of compensation for their time on the committee (ICMR 2006), "under no circumstances may payment be offered or accepted for a review committee's approval or clearance of a protocol" (CIOMS 2002, Guideline 2:24).

2. Membership structure of an IEC

In addition to the Chairperson, the IEC should have a Member Secretary from within the institution who is responsible for the administrative tasks of the committee (ICMR 2006). The rest of the IEC should comprise a multidisciplinary team of members—both affiliated and non-affiliated to the institution—that represent medical and non-medical, scientific and non-scientific backgrounds. Similar to the U.S Common Rule requirements for membership to IECs, Indian regulations also require the IEC to have "at least one member whose primary area of interest/specialization is non-scientific and at least one member who is independent of the institution/trial site" (Schedule Y, amended 2005, The Drugs and Cosmetics Rules 1945).

The recommended composition of an IEC is (ICMR 2006):

- One Chairperson
- One Member Secretary
- One or two basic medical scientists
- One or two clinicians
- One legal expert or retired judge
- One social scientist/representative of a non-governmental voluntary agency

- One philosopher/ethicist/theologian
- One lay person from the community

"With adequate representation of age and gender to safeguard the interests and welfare of all sections of the community/society" (ICMR 2006:10), the size of an ethics committee should not exceed 12 to 15 members to avoid difficulties in reaching a consensus (Indian GCP n.d.), with the minimum number of members being seven (Schedule Y, amended 2005, The Drugs and Cosmetics Rules 1945).

Ethics committee meetings also require a quorum of at least five members with one member, representing each of the following professional backgrounds (Schedule Y, amended 2005, The Drugs and Cosmetics Rules 1945).

- Basic medical scientist
- Clinician
- Legal expert
- Social scientist/ethicist/ NGO representative/theologian
- Lay person or community representative

An IEC can also invite experts to assist ethics committee members on specific areas such as a cardiologist for cardiac disorders or a pediatrician for clinical trials that have children as trial subjects.

While ethics committees need to comply with ethical guidelines and regulations, every IEC must establish its own SOP so it can function effectively and independently within its associated institution (Levine 1988; ICMR 2006). The SOP should be given to every member. It should include information on the institution's policy regarding the terms of appointment, dismissal and resignation of members. The SOP should also state the systems in place for ethics committee meeting schedules, honorarium to members and other information such as a processing fee charged to investigators of clinical trials.

Although the focus of this study is the IEC, the ICMR guidelines also apply to independent ethics committees that are used by private physician-investigators unaffiliated to an institution or by institutions who do not have an IEC. While the ICMR recommends that smaller institutions can approach a registered Institutional

Ethics Committee or an independent ethics committee (ICMR 2006) there is currently no mandatory registration for institutional or independent IECs.

3. Review Procedures of the IEC

- **Scientific and ethical review of a research protocol**

For an IEC to achieve its goal of applying the fundamental ethical principles of Respect for Persons, Justice and Beneficence, in the protection of the human research subject, it has to follow certain prescribed procedures to ensure the scientific and ethical integrity of a research protocol. The IEC is therefore responsible for both the scientific and ethical review of the proposed research. A scientific review will include an assessment of:

a) Purpose of study
b) Scientific value of the study
c) Research methodology
d) Appropriateness of scientific design

An ethical review of a protocol will include an assessment of:

a) Equitable selection of research subjects
b) Exclusion and inclusion criteria for selection of research subjects
c) Minimization of risks posed by the study
d) Community consultation
e) Informed consent
f) Standards of care provision
g) Incentives given to trial subjects
h) Compensation for research related injuries
i) Access to research benefits post-trial

According to ICMR "it is advisable to have separate Committees for each [kind of review], taking care that the scientific review precedes the scrutiny for ethical issues (ICMR 2006: 8). The CIOMS guidelines, which also give ethics committees the option for not carrying out the scientific assessment of a protocol, do however, recommend that ethics committees undertake both the scientific and ethical reviews because the two kinds of reviews "cannot be separated: scientifically unsound research involving humans as subjects is *ipso facto* unethical in that it may expose them to risk or inconvenience to no purpose; even if there is no risk of injury, wasting

of subjects' and researchers' time in unproductive activities represents loss of valuable resource. Normally, therefore, an ethical review committee considers both the scientific and the ethical aspects of proposed research" (CIOMS 2002, Guideline 2: 25). Those IECs that are not responsible for the scientific review nevertheless also review a protocol for its scientific and technical merits. In some cases it is the scientific design in itself that is ethically problematic. For example, in the case of a RCT, consent procedures can be complicated, as patients hoping to receive benefit from an experimental therapy will have to be informed about the possibility of being placed in a placebo arm. The investigator also has to justify his use of a RCT, honestly stating the null hypothesis: that there is no scientifically valid reason that Therapy A will be any better than Therapy B and that there is no known Therapy C that is better than Therapies A or B, unless there is good reason for the investigator to not use Therapy C (Levine 1988: 187).

The review of protocols is done in scheduled meetings and decisions should not be taken through an informal circulation of proposals among IEC members. The IEC, according to ICMR guidelines, must meet at regular intervals and should communicate its decision regarding a protocol within three to six months of receiving it (ICMR 2006).

4. Components of ethical review

An IEC must first conduct an initial review followed by an on-going review of research that has already been approved. All communication regarding the proposed and approved research is usually via the investigator and not the sponsor of the trial. The information that the investigator is required to submit to the IEC for initial review of a clinical trial protocol is based on a prescribed format and should include the following components (Indian GCP n.d.; ICMR 2006):

- **General information on the investigator and sponsor**

The investigator needs to provide the IEC with details of the sponsor or the funding agency of the trial and or the CRO involved. Information on the Primary Investigators/co-investigators contact information, qualifications and experience in clinical research is also given to the IEC.

- **Conflict of interest**

The IEC is responsible for advising investigators on the consequences of any conflict

of interest and the potential harm it could cause to trial subjects or the ethical integrity of the research proposed. The ICMR defines conflict of interest 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 is termed as Conflict of Interest" (ICMR 2006: 26). Conflict of interest is of particular concern when investigators have business interests with commercial enterprises or drug companies who are involved with the trial or when the pharmaceutical industry offers attractive incentives such as stock options, a consultancy fee and international travel to induce physician-investigators into conducting the clinical trial.

- **Research objectives**

Information on the objectives of research should include the goals of the study and its rationale for using human subjects in the context of existing knowledge on the proposed intervention and the phase of the clinical trial.

- **Publishing outcomes of research**

An investigator must explicitly state the sponsor's policy for publishing both negative and positive outcomes of the research and ensuring the privacy of the trial subjects in the publication.

- **Study methodology and study treatments**

An investigator must state if the study, for example, is a double blinded or single-blinded RCT. The trial's treatments such as dosage, the route of administration and the time frame for both the intervention being studied and for the product being used as a control needs to be explained. The investigator must also provide information on any invasive procedures that will be performed during the trial and the ethical justification for using certain methodologies such as placebo controls.

- **Standard of care**

The investigator is required to have a strategy on withdrawing or withholding the standard therapy in the course of research.

- **Safety information**

The IEC needs to review existing safety information of the drug or vaccine to be tested including relevant results from non-clinical studies or animal research as well as data from clinical research.

- **Methods used to recruit trial subjects**

The guidelines state that an IEC should ensure that the process of selecting trial

subjects must be equitable. That risks and benefits of research should be equally distributed and "persons who are economically or socially disadvantaged should not be used to benefit those who are better off than them" (ICMR 2006: 28). The investigator needs to inform the IEC if the trial subjects are patients or healthy volunteers and if their selection has been based on age, sex and gender or if any diagnostic criteria have been used for their selection or exclusion (Indian GCP n.d.). The ICMR has specific guidelines on the selection of "special groups" such as pregnant or nursing women, children and vulnerable groups. Pregnant women or nursing mothers are not permitted to be recruited as trial subjects unless the research poses "no more than minimal risk (discussed later in this chapter) to the fetus or nursing infant..." (ICMR 2006: 27) and the research is being conducted specifically to obtain new knowledge for the advancement of maternal health, neonatal health or that of the unborn child. The use of this category of subject can only be justified in certain kinds of trials—those conducted to reduce mother to child transmission of HIV, or to identify fetal abnormalities and for other pregnancy related conditions—in which women "should not be deprived arbitrarily of the opportunity to benefit from investigations, drugs, vaccines or other agents that promise therapeutic or preventive benefits (ICMR 2006: 27).

Regarding the selection of minor research subjects, the IEC should ensure that "children will not be involved in research that could be carried out equally well with adults" (ICMR 2006: 28). An investigator can test a new drug on children only after a Phase III clinical trial using adult subjects has been completed. An earlier phase can be conducted using children only if the drug has therapeutic advantages that are relevant to a primary disease of children and if the risks posed to minors can be justified in light of the anticipated benefits. A child's refusal to participate in a clinical trial "must always be respected unless there is no medically acceptable alternative to the therapy provided/tested, provided the consent has been obtained from parents/guardian" (ICMR 2006: 28).

Vulnerable groups are those with reduced autonomy who have limited or no agency to make a judicious assessment of the risks and benefits of a trial or are those sections of the population who can be potentially coerced into participating in a trial. These vulnerable groups include the mentally challenged, prisoners, students,

subordinate employees and those who are socially and economically disadvantaged.

- **Assessment of risk and benefit**

There are three levels of review that an IEC can select at the time of assessing an investigator's protocol: exempted review, expedited review or a full review (ICMR 2006). The categorization of the protocol into either of these review options is dependent on the level of risk posed to the trial subjects that the IEC must examine in the context of the anticipated benefits of the research—one of the most fundamental tasks of an IEC. 'Risk' can be defined as the probability of harm or injury to the trial subject occurring as a result of participation in clinical research and 'benefit' can be defined as "something of value", an advantage or something that is desired from the research. (Levine 1988: 37). The probability of harm or injury can be defined in quantitative terms such as either a large harm or a small harm. Terms such as small risk or harm, Levine states are however ambiguous and could imply that the probability of an "unspecified amount of harm" is small or it could mean that the probability of "a small amount of harm" occurring is not determined (Levine 1988: 37).

The IEC needs to assess whether the risks presented in a research protocol can be justified to the trial subject in light of the benefits accrued to a trial subject by participating in a clinical trial or to society in general. All ethical guidelines—both national and international—stress the importance of ethics committees ensuring a favourable balance between the risks and benefits of research and "without such a favorable balance there is no justification for beginning the research" (Levine 1988: 38). The assessment of the risks and benefits of a clinical trial is thus, one of the major responsibilities of an IEC:

> If the ethical review committee finds a research proposal scientifically sound, or verifies that a competent expert body has found it so, it should then consider whether any known or possible risks to the subjects are justified by the expected benefits...and whether the proposed research methods will minimize harm and maximize benefit...If the proposal is sound and the balance of risks to anticipated benefits is reasonable, the committee should then determine whether the procedures proposed for obtaining informed consent are satisfactory and those proposed for the selection of subjects are equitable (CIOMS 2002, Guideline 2: 25).
>
> The [ethics] Committee should evaluate the possible risks to the participants with proper justification, the expected benefits and adequacy of

documentation for ensuring privacy, confidentiality and justice issues (ICMR 2006: 11).

This key task of an IEC derives from the three ethical principles of Respect for Persons, Beneficence and Justice. Research that involves human subjects should be beneficial to them or the community and all research subjects should have the right to know about the potential risks and benefits of the research so that they can make a well-informed decision about whether to consent to a trial or not. Providing potential trial subjects a complete picture of the risks and benefits of proposed research also enables the selection of research subjects on the basis of redistributive justice, giving them an opportunity to be fully aware of the possible burdens involved in the research (Levine 1988).

a) Levels of risk

There are three levels of risk stated in both national and international guidelines and regulations: minimal risk, less than minimal risk and more than minimal risk. The only kind of risk defined in the ICMR guidelines and also other international regulations such as the U.S. federal regulations is minimal risk (HHS, OHRP 1993). Minimal risk is "defined as one which may be anticipated as harm or discomfort not greater than that encountered in routine daily life activities of [the] general population or during the performance of routine physical or psychological examinations or tests" (ICMR 2006: 11).

Protocols that do not involve invasive investigations and require a study of existing data, or those protocols that propose to use educational tests, surveys or interviews, and present less than minimal risk can be exempt from IEC review. Protocols that pose only minimal risk for trial subjects can be examined under the expedite review option. Expedited protocols can be amended protocols or changes made to protocols after they have been examined by the IEC using full review procedures. Continuing review of approved research that poses no additional risks can also expedited by the IEC. Research on drugs that have already been approved and are not using vulnerable populations can also be expedited. At the time of disease outbreaks or disasters, a protocol can be expedited and an intervention can be tested with written permission from an IEC. For expedited reviews, the Member Secretary, the Chairperson or a specific member can be made responsible for examining a protocol without convening an IEC meeting (ICMR 2006). With regard to a full review, all those protocols that

present more than minimal risk, use vulnerable populations and those that do not qualify for exempted or expedited review need to undergo a full review by the IEC.

b) Categories of risk and benefit

Levine defines three categories of risk: physical, psychological, social and economic (Levine 1988). In the case of physical risks, Levine states that in most research, physical risk is "mere inconvenience" (Levine 1988:41) that a trial subject has to face such as the withdrawing of blood or providing a urine sample. Trial subjects may also experience minor discomforts that are temporary in nature such as dizzy spells, or the withdrawal of venous blood that can be painful but for a short period of time. On the other hand, research that is assessing a new drug or procedure can present risk that is more than minimal and can lead to permanent disabilities and death. For those protocols that require a full review, presenting physical risk that is more than minimal risk to trial subjects, the IEC should assess the invasive procedures that will be used and the facilities available at the trial site to perform those procedures. For example, the ICMR guidelines recommend that in the full review of a protocol, an IEC should ensure that the withdrawal of blood from healthy adults and women who are not pregnant, and whose weight falls within the normal range, should not be more than 500 ml of blood within an eight-week period and the withdrawal of blood should not be done more than twice a week (ICMR 2006). Psychological risks include feelings of depression, episodes of hallucination and confusion as a result of a drug that is administered to the trial subject. Majority of psychological risks are temporary but the IEC should be cautious in its determination of such risks as they have the potential to cause serious psychological damage to a trial subject. Social harm can occur when a trial subject's privacy is invaded in the course research or if confidential records are made public without the subject's knowledge causing embarrassment, guilt or stress. Economic risks are costs that a trial subject may have to incur due to participation in a trial such as hospitalization, travel to the trial site and loss of wages (Levine 1988: HHS, OHRP 1993).

Benefits from research can be broadly divided into direct benefits for the trial subject and benefit to society. With regard to direct benefits, for example, an intervention could treat or improve the condition a trial subject is suffering from. With regard to benefit to society, the research could increase the general understanding of a

condition, enhance the safety of a drug being tested or improve current technology (HHS, OHRP 1993).

Levine defines three kinds of direct benefits to a trial subject: economic, psychosocial and kinship benefits (Levine 1988). Psychosocial benefits can be experienced, for example, by cancer patients who have tried all the available therapy without success, and are willing to participate in a trial in the anticipation of trying out an investigational drug that might offer them some relief and who otherwise may not be able to afford or access the experimental treatment. Individuals may participate in a trial out of a sense of altruism and the need to increase their sense of self worth (Levine 1988). Kinship benefits can be those choices that individuals might make to share the burden of research with the objective of relieving the suffering of a close friend or relative. Economic benefit refers to cash payments offered to trial subjects for participating in a trial. Levine states that some "impoverished" individuals might think it necessary to "assume extraordinary risk or inconvenience in order to secure money or other economic benefits that will enable them to purchase what they consider the necessities of life" (Levine 1988: 82) While guidelines state that payment for transport costs or payment for compensation of loss of working hours should not be considered as benefit and payments should be kept reasonable so that they do not become undue inducements, there is no explanation on about due or undue inducements.

c) Minimizing risk

The investigator needs to provide the IEC sufficient explanation of magnitude of harm and how long that harm will have to be suffered by the trial subject. An IEC is responsible for ensuring that the risks presented are minimized as much as possible. The committee needs to assess an investigator's relationship with trial subjects, because if an investigator is also the treating physician, the physician-investigator could prioritize the research interests and encourage a subject to participate in a trial even though the research may not be beneficial to the subject.

The IEC must also examine the research design in to minimize the potential for risk.

> The medical management of the adverse event is the responsibility of the investigator, and the protocol for adverse event management with allocation of responsibilities must be pre-defined in the protocol and submitted to the Ethics Committee (ICMR 2006: 43).

For example, some potentially serious risks can be avoided if they are detected early and if a timely intervention is made in the form of treatment. The IEC needs to study the procedures an investigator will follow for the early detection and management of potential harms and the criteria used to make a decision to stop the research or to provide an antidote. In the case of a double-blinded, RCT where the investigator is not aware of a subject's treatment and in the course of the trial the subject's condition can deteriorate due to the intervention or an unrelated condition, the protocol needs to be studied to see if there is a mechanism in place to safeguard against such occurrences (HHS, OHRP 1993).

d) Maximizing benefit and post-trial access

While harms in research should be minimized, the benefits of research should also be maximized for trial subjects. The IEC needs to assess for how long trial subjects can enjoy and access the benefits of a particular procedure or investigation. For example, the sponsor may discontinue a drug that may have proven to be beneficial or effective to a trial subject after the trial because the drug was found to be beneficial to only a small number of patients, therefore making it too expensive for the drug company to produce. On the other hand, the drug that was beneficial to a trial subject during the trial might be unaffordable to the individual and the community after the trial (Levine 1988). With specific reference to drug trials, where a drug is found to be effective ICMR states that "it should be made mandatory that the sponsoring agency should provide the drug to the patient till it is marketed in the country and thereafter at a reduced rate for the participants whenever possible" (ICMR 2006: 36). The ICMR guidelines state that ethics committees should also consider post trial benefits for the community in the form establishing schools, clinics or counselling centres, in the *a priori* agreement of the sponsor.

If the research proposal offers no direct benefit to trial subjects, then the IEC should assess if the investigations involved to create generalizable knowledge for the benefit of society can be ethically justified, as the risks individuals should undergo for the benefit of society should have certain limitations.

e) Risk and benefit in the context of selecting trial subjects

The IEC should also evaluate the balance of harm and benefit in the context of selecting trial subjects. In the context of harm, the committee should ask if there is a way to identify individuals who are more susceptible to those harms? If the

individuals are identified, will they be informed about their susceptibility to those harms and will they be excluded from the clinical trial? On the other hand, while considering benefit, will those individuals who are most likely to benefit from the research be identified and will those individuals be included in the trial as they are most likely to benefit, and therefore excluding those persons who may not benefit from the research (Levine 1988).

- **Informed consent**

Regarding the process of obtaining consent, an investigator is required under the Rules to "provide information about the study verbally as well as using a patient information sheet, in a language that is non-technical and understandable by the study subject" (Schedule Y, amended 2005, The Drugs and Cosmetics Rules 1945). The IEC must examine the informed consent documents—patient information sheet and informed consent form—for the content and level of readability so that trial subjects can make a well-informed and well-understood decision about consenting or refusing to participate in a clinical trial. The patient information sheet that should include the following elements:

a) Nature and purpose of the study.

b) Explanation of any other suitable alternative therapies available.

c) Duration of the study.

d) Procedures and investigations that the trial subject will have to undergo in the course of the trial.

e) An explanation of the treatment arms of the trial such as a placebo arm.

f) The anticipated benefits of the study or the positive outcome of the research that can be expected by trial subjects. If no benefits are expected the trial subject must be informed. With reference to drug trials, the ICMR states that the investigator-physician should ensure that the trial subjects are aware of the difference between therapy and research at all times and that the drug being administered to them is experimental and therefore the benefits are yet to be proven (ICMR 2006).

g) Foreseeable risks or discomforts that the trial subject might have to endure as the result of participating in the trial.

h) The plan for managing risks that are more than minimal and compensating and/ or treating trial subjects in case of injuries that occur in the course of a trial.

i) Right of the trial subject to withdraw from the trial at any point in time without fear of denial of on-going treatment if the investigator is also the subject's physician.

j) Payments to trial subjects for participation.

k) Information on new findings that may develop in the course of the trial that can alter a trial subject's decision to continue participation.

l) Access to beneficial outcomes after the trial is over.

m) Identities and contact information of the research team.

n) Contact information of the Chairperson of the IEC in case trial subjects need to report any violations.

In addition to examining informed consent documents, the IEC must also insure that the procedure of informed consent is an on-going process that involves a series of steps and not a one-time procedure of signing an informed consent form (HHS, OHRP 1993).

The process of obtaining informed consent of 'special groups' needs greater consideration by the investigator and the IEC. In the case of consent from children, the parent or legal guardian of the child must give proxy consent. Consent for those individuals who are mentally challenged and are incapable of making decisions for themselves should be taken from their legal guardians who should be informed of all the aspects of the trial. Although the requirement of informed consent is based on the ethical principle of Respect for Persons and the requirement of an equitable selection of trial subjects is based on the ethical principle of justice, in the case of vulnerable persons or those who do not have the power, resources, intelligence and strength to protect their own interests in the negotiation of informed consent, there is an "interplay" between the two ethical principles (Levine 1988: 72).

Verbal or oral consent is permissible in the presence of an "unrelated witness" or a third party, if a trial subject is unable to consent with a signature or a thumb impression or if written consent in a "sensitive" trial could potentially threaten the subject's privacy. In the case of a drug trial, if an individual can only provide a thumb impression, an unrelated witness needs to sign the consent document and another thumb impression of a relative or legal guardian of the trial subject should not be accepted (ICMR 2006: 22).

In certain situations, informed consent requirements can be waived: if the research presents risks that are less than minimal, if research is undertaken in emergency

situations, or if the trial subject does not come into contact with the investigator.

- **Compensation for research related injury**

The IEC is required to assess the sponsor/investigator's provisions for compensation in the form of free treatment or insurance cover or monetary compensation to the trial subject for research related injury or adverse events and compensation to families in the case of death. The ICMR guidelines state that the sponsor of the research, regardless of whether it is a drug company, a private institution, or a government agency, should in a "*a priori* agreement" state the compensation provided for physical and psychological injuries and also insurance cover for "unforeseen injury whenever possible" (ICMR 2006: 29).

- **Policy for monetary and non-monetary payments to trial subjects**

Trial subjects can be compensated for the time and inconvenience faced due to participation in the trial. This compensation can be in the form of cash payment for travel to the trial site and free ancillary treatment or referrals. This kind of practical compensation should not be confused with benefits. However, the compensation provided should be within reasonable limits in order to avoid undue inducement or unfair manipulation of an individual who then might be coerced into participation in a trial against his or her better judgment.

5. Continuing review and monitoring of clinical trials

After a clinical trial has been approved, the IEC is also responsible for continued assessment of a clinical trial to ensure that the mechanisms for subject protection in the initial review are sustained as the trial progresses. The role of continued review and monitoring of approved research by IECs are explicitly stated in national and international guidelines and regulations:

> The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of its progress (CIOMS 2002, Guideline 2:24)
>
> Ethics Committees are entrusted not only with the initial review of the proposed research protocols prior to initiation of the projects but also have to have a continuing responsibility of regular monitoring of the approved programmes to foresee the compliance of the ethics during the period of the project (ICMR 2006: 8)

Continued review of a clinical trial involves the IEC examining annual reports, adverse event reports and any amendments to a protocol—all of which are sent to the

IEC by the investigator. The ongoing research can be reviewed once in six months or once a year by the IEC. The terms of the progress reports should be specified in the SOP of the IEC and continued review "may be based on the periodic study progress reports furnished by the investigators and/ or monitoring and internal audit reports furnished by the Sponsor and/or by visiting the study sites" (Schedule Y, amended 2005, The Drugs and Cosmetics Rules 1945). The occurrence of serious adverse events during a trial must be reported to the IEC within seven days of the event occurring. The IEC also needs to review adverse event reports to ensure that the balance of risk and benefit at the time of initial review has not changed and is still safe for trial subjects.

6. Administrative responsibilities

In addition to the initial and continued review of clinical trial protocols the IEC, particularly the Member Secretary is also responsible for the documentation of all communication with investigators, archiving protocols, keeping minutes and agendas of IEC meetings, preparing Standard Operating Procedures and the storage of other relevant records related to the work of the ethics committee. These records should be preserved for a period of at least three years. The ICMR guidelines recommend full time secretarial staff and an office space for the efficient functioning of an IEC (ICMR 2006).

7. Clinical trial registration

India established its Clinical Trial Registry of India (CTRI) in 2007 and became a Partner Registry of the International Clinical Trials Registry Platform established by the WHO in the year 2004 with the objective of achieving transparency in the clinical trial process. The International Committee of Medical Journal Editors (ICMJE) supported the WHO initiative and declared that the research community is obligated to report any unfavourable outcomes of clinical trials, as typically sponsors censor the publication of negative data. The ICMJE also stated that it would not consider research for publication unless the clinical trial is registered in a publicly accessible registry (*Evidence-based Obstetrics and Gynecology* 2006; Petryna 2009). All ethics committees in India need to ensure the prospective registration of clinical trials on the CTRI website and ethics committees are also expected to disclose their details on the registry. Although registration is free and voluntary it will only be valid if the

information provided complies with the list of twenty items on the WHO Trial Registration Data Set. While India endorsed the "scientific and ethical imperative" of free public access to clinical research, the registration is not mandatory. In the absence of regulation, the ethics committees, can, however ensure clinical trial registration by giving only temporary ethical clearance to a research protocol until it has been registered on the CTRI (Tharyan and Ghersi 2008).

II. Problems in Implementing The Role of an IEC

1. Informed consent

The IEC is the key regulatory mechanism to ensure that the process of informed consent abides both in letter and spirit to the ethical principle of Respect for Persons. Informed consent first formalized and prioritized by the Nuremberg Code and later adopted by national and international regulations for biomedical research on human subjects is today a necessary requirement of clinical research. "It is through informed consent that the investigator and the subject enter into a relationship, defining mutual expectations and their limits...they are obligated to inform the lay person of the consequences of their mutual agreements" (Levine 1988: 98).

This imperative of informed consent, a fundamental requirement in ethical regulation of research, has however been widely critiqued for several reasons. The guidelines and regulations that iterate the necessity for respecting an individual's autonomy while explicitly stating the procedures and requirements of acquiring and documenting informed consent, fail to emphasize the importance of evaluating the trial subject's comprehension of the information after his or her interaction with the investigator (Bhutta 2004). "Informed consent is not valid unless the consentor comprehends the information upon which consent is based" (Levine 1988: 119). The application of the ethical norm of informed consent, while easy to state in a regulation or guideline is a challenge to achieve in practice (HHS, OHRP 1993). Members of IECs who volunteer their time, in addition to their regular jobs and are burdened with an increasing number of protocols to review and administrative requirements of institutions, rarely leave the confines of their committee room to visit a trial site to actually observe what happens in the informed consent process (Edgar and Rothman 1995:493). Institutional Ethics Committees, therefore have no interaction with potential research subjects to ensure that they have understood the information about

the trial before they agree to give their consent. The IEC also has no supervision mechanism in place to ensure that the investigator has respected the trial subject's right to make a decision that is free of coercion or any kind of pressure to participate in the clinical trial.

The examination of informed consent documents is essential because it is through the consent document that the ethics committee is made aware of the kind of information that the trial subject will have to process before a decision is made. The focus on procedural issues around informed consent however, critics argue, detracts from the unequal contexts of clinical trials (Petryna 2009). Informed consent is treated as "an ethical panacea", a solution to counteract the autocratic and paternalistic medical expert that conceptualizes an individual as an autonomous individual functioning in isolation of his or her social and economic context (Corrigan 2003: 768). For instance, when an individual makes a decision to consent to participate in a clinical trial, the decision is guided by other factors such as the person's implicit trust in his or her physician or medical expert, the person's need to please the doctor and in the person's faith in the progress of science and medicine. When a patient is asked by the treating physician to participate in a trial, the patient has certain expectations and assumptions of the physician not as a researcher in a trial, but as the patient's doctor who will act in the best interest of the patient (Levine 1988; Corrigan 2003). The patient is looking for advice and reassurance from the doctor, especially in developing countries like India, where the doctor is also usually the investigator and patients in their desperation for treatment may have little choice in refusing to participate in their physician's research project (Katz 1996) and mistake the research for treatment. In addition, prospective trial subjects can find it difficult to understand the inherent risks of a particular research design used in clinical trials. For example, a systematic review done on patient comprehension of the randomized control trial—the preferred method in drug and vaccine trial in which every patient has an equal chance of being assigned to any one of the treatment arms—indicated that patients have a limited understanding of random allocation (Edwards *et al* 1998 cited in Kerr *et al* 2004:80) and expect that "physicians will provide advice based upon their personal knowledge of the patient, his or her ailment, and of therapeutics" (Levine 1988: 194). The consent form in such situations means little except a requirement that the investigator has to fulfil to get the 'go-ahead' sign from the IEC. Ethics committee members have access to only the

written information given to the patient by the physician-investigator even though the communication between the physician-investigator and the patient about the research is also done orally. Studies conducted in the U.K., in which physician-investigators were questioned about the content of the conversation with their patients, have revealed that doctors spend little time explaining research design to their patients and tend to focus more on those aspects of the research that patients will comprehend with greater ease (Karr *et al* 2004). "Patients frequently have over-riding emotional and physical needs. Depending on their condition and stage of ill health, they often experience pain, shock and anxiety and it cannot simply be assumed that the imposition of the informed consent process will necessarily bring about an equitable doctor-patient relationship where patients make active choices" (Corrigan 2003: 788).

The current form of informed consent has been widely criticised for having taken centre stage in the discourse of human subject protection in clinical research. The guidelines and regulations for the protection of human subjects in clinical research, that describe the detail of informed consent procedures and the requirements of disclosure to the trial subject by the investigator, have promoted the creation of a "consent-based regulatory model for biomedical and behavioural research" (Petryna 2009:67). Institutional Ethics Committees are faulted for spending more time on the consent form rather than the negotiations involved in informed consent and other ethical considerations such as the equitable selection of subjects (Levine 1988) and on questions regarding trial subject access to an effective drug after a trial is over (Corrigan 2003). The consent forms themselves are in fact instruments that have been designed to protect the investigator, sponsor and the institution from liability rather than for the interests of the human subject (Levine 1988).

The domination of the Principle of Respect for Persons over other ethical principles is a reflection of the increasing importance given to the idea of individualism in Western liberalism (Corrigan 2003: 770) and the neo-liberal doctrine of making people assume responsibility for their own well being by encouraging personal 'choice' and 'freedom' (Harvey 2005). "It is through informed consent that we make operational our duty to respect the rights of others to be self-determining, i.e., to be left alone or to make free choices" (Levine 1988: 96). The question raised, especially in the context of trial subjects in the developing world, is the validity of free and fair

informed consent when a decision has the potential to be based on a forced choice in a circumstance of destitution and oppression (Macklin 2003). Illiteracy, combined with an implicit trust for ones primary physician, can make people sign documents without understanding the repercussions of consent. For, example, documentary evidence from the HPV trials in India clearly indicates a violation of informed consent regulations and the lack of IEC supervision of the informed consent process. An investigation of the HPV trials indicated that hostel wardens or head masters of the girls' schools signed approximately 2,763 informed consent forms of a total of 14,253 (Sarojini *et al* 2011:18). This process of consent grossly violated the major informed consent regulation for minors and other special sections of the population, that explicitly states the requirement of a "legally acceptable representative" of the trial subject, or an "impartial witness who should be present during the entire informed consent process" if the legal representative is unable to read or write (Schedule Y, amended 2005, The Drugs and Cosmetics Rules 1945).

The current model of informed consent if of great concern in the context of the multinational clinical trials conducted in developing countries today, where "virtually any kind of research is often seen as ethically permissible as long as individuals have given informed consent" (Shushter 1998: 977). While, giving individuals the opportunity to exercise their decision making abilities is an integral consideration of clinical research, the consent-centric framework in its current form is a narrow one, which allows an investigator to merely provide documentary proof of the potential subject's consent to participation in research leaving the entire responsibility of consent to the subject's judgement of the proposed research and its potential risks and harms. If the documentary evidence is adequate then no external authority can claim that the consent process failed to comply with legal and ethical requirements (Petryna 2009). The current understanding of informed consent therefore needs to be broadened and the arguments for its importance need to be more nuanced.

2. The risks and benefits of research

The role of evaluating the risks and benefits of a protocol has assumed grave importance today because of the sheer number of clinical trials being run, exposing larger numbers of research subjects to the potential of harm. The expansion of clinical trial operations from the West to the developing world, the unregulated growth of

independent ethics committees, private clinics and CROs who are all involved in the clinical trial process, have made clinical research a risky business demanding closer attention by independent review (Kimmelman 2004).

Despite the assessment of risk and benefit being central to the protection of trial subjects, the guidance available for IECs on evaluating risks and benefits of research is limited and nebulous. Jesani states that the Indian guidelines on the protection of human subjects in biomedical research give the practical and operational issues greater weight and neglect ethical concerns such as the complicated issue or risks in relation to benefits associated with a trial (Jesani 2010). Charles Weijer and Paul B. Miller—from the Bioethics Department of Dalhousie University in Canada—argue that unexplained guidelines "often provoke more questions than they answer. Which risks to subjects must be minimized? To what extent must they be minimized? Which risks and which potential benefits are to be considered in the reasonableness determinations? By what measure does one determine that risks are reasonable in relation to benefits to subjects?" (Weijer and Miller 2004:570).

Jonathan Kimmelman states that there can be no universal agreement on the definition of minimal risk because risks that are encountered in ones daily life can be perceived differently by trial subjects and ethics committee members. Kimmelman adds that the dominant understanding of risk, that uses terms such as 'minimal', 'probability' and 'magnitude' in relation to risk and benefit assessment have reduced the understanding of risk and benefit evaluation to only a technical and quantifiable understanding to be done by experts. This definition of risk does not include the social contexts of those being exposed to harm and of those assessing the harm and subjective interpretations or risk. For example, an individual might agree to participate in a trial on the basis of his or her understanding of risk and benefit that differs from the investigator's or the IEC member's understanding. Or a trial subject's perception of the risks involved might be less serious than the assessment of the IEC because of the trial subject's trust in the physician-investigator's judgment of risk and faith in the institution where the research is being conducted. Therefore, Kimmelman states that the understanding of risk must be understood not only within the confines of research procedures or interventions but should also include the "social dimensions of risk" (Kimmelman 2004: 378) so that "lay risk rationalities" can be incorporated into the process of

reviewing clinical trial protocols (Kimmelman 2004:384). The ICMR guidelines recommend that IECs appoint representatives of patient groups to assist the committee in safeguarding the interests of the trial subjects. There is no evidence to suggest that IECs do in fact appoint representatives of research subjects' communities who can bring the IEC closer to a trial subjects perception of risks and benefits of a trial (ICMR 2006). Kimmelman however advises caution in this approach and adds that a balance between the technical review of risk and the lay review of risk needs to be ensured (Kimmelman 2004).

3. Continuing review and monitoring of clinical trials

While periodic reports and adverse event reports from the trial site are sent to the IEC by the investigator, other monitoring activities require ethics committee members to make site visits. Continuing review of approved research can function as an important safety mechanism as many research subjects can sign consent forms with limited comprehension or knowledge of the risks involved (HHS, Office of Inspector General 1998). In addition to monitoring the informed consent process, a site visit is essential for the IEC to examine if the investigator has made any amendments to the ongoing research without ethics committee approval or if trial subjects have been exposed to unnecessary risks and if investigators have been carrying out any other unapproved research at the site.

The inspection of ethics committees by the Office of Inspector General of the HHS in the U.S. found that continued review by ethics committees is largely confined to paper work:

> On those few occasions when IRBs do become more directly involved in reviewing a research practice, the action tends to be triggered more by particular concerns that have come to their attention than by random reviews. (Note 28) As a result, IRBs typically have little basis to know for themselves how research teams approach the informed consent process, how well human subjects understand the implications of their participation in research, and how fully research teams remain true to the research design set forth in their approved protocols. (Note 29) (HHS, Office of Inspector General 1998).

Levine acknowledges the importance of on-site monitoring of approved research but believes that the IECs should not function as a "police force" and site visits by IEC members should take place for supervision of only certain functions such as informed consent (Levine 1988: 348). Policing the activities of investigators by IECs, according

to Levine, is an indication that ethics committee members are working on the assumption of distrust of the research community and "the incessant harassment of the majority of investigators in the interest of finding the occasional wrongdoer" is unnecessary. This assumption of suspicion and distrust will cost the IEC its credibility and its reliance on an informal network of reporting by students, doctors and nurses. Levine makes his point in the context of the academic research community but argues that his "presumptions of trust" (Levine 1988:349) must also extend to other communities.

Levine's argument may not hold true in a country like India where the role of monitoring clinical trials by an IEC or by another regulatory body remains a compulsion due to the country's uneven and unaccountable system of clinical research and ethical review.

4. Compensation for research related injuries

Regarding safeguards in the form of insurance and other means of compensation for trial subjects in case of minor risks or serious adverse events suffered is an issue that has been debated but not given enough emphasis in ethical guidelines. There is no well-defined policy in India for compensating trial subjects when they are exposed to risks or harms in the course of a clinical trial and the current methods used to tackle trial-related injuries by ethics committees and institutions are therefore arbitrary. One view on compensation for research related injuries—indicated in U.S regulations for human subject protection—is that sponsors/institutions should not be made responsible for injury-related compensation or free medical treatment because trial subjects agree to participate in research only after they are made aware of the risks involved. Proponents of this view also contend that injury-related compensation is also complicated because it is difficult to assess whether the injury resulted from the trial itself or from other risk factors particular to the trial subject (Steinbrook 2006). On the other hand, in European countries where there are stricter laws on universal health insurance for citizens, trial subjects have greater protection for research-related injuries. In 2001, the European directive on clinical trials declared that no trial is allowed to be conducted unless provisions have been made by investigators and sponsors, for insurance or indemnity, regardless of whose fault it is (Steinbrook 2006). In India, on the other hand, where the majority of the people are uninsured and

there in no legally binding requirement for clinical trials sponsors to ensure compensation, the ICMR guidelines can only recommend to the sponsor that it is their moral imperative to provide compensation to research subjects for any physical or psychological injury suffered in the course of the trial.

Guidance for deciding the size of compensation, duration of compensation and the category of compensation based on the degree and seriousness of injury and guidelines on managing deaths in a clinical trial is not available to the IEC. The matter of compensation is therefore left to the discretion of the IEC, although the ICMR does suggest the option of an "arbitration committee or appellate authority" that could be established by institutions to manage compensation issues, especially in the case of large clinical trials (ICMR 2006: 29). Having an institutional policy in place, however, does not necessarily indicate what happens to a trial subject after an injury occurs (Steinbrook 2006).

A study, conducted by U.M. Thatte and others to assess the knowledge of compensation related injury among the different stakeholders in clinical trials in India, that included investigators and ethics committees, found that only 40 percent of investigators and 30 percent of ethics committee members stated that their institutions had policies for compensation to trial subjects in case of research related injuries. A majority of the respondents stated that their institutions had no mechanism for grievance redressal or arbitration for the injured trial subject. The ethics committee members of the study also stated that while they insist that the investigators/sponsors provide the committee with their plan for compensation, the ethics committee members did not have the time or the expertise to closely examine the compensation related documents. While all the stakeholders agreed that the sponsor should be accountable for compensation, 67 percent of the investigators and 48 percent of the ethics committee members stated that when a trial related injury occurred, the trial subjects or their relatives had to first pay for management of the injury and were reimbursed later, but only on evidence of payment. In case of compensation due to a death in the course of the trial, both investigators and ethics committee members stated that they had no policy in place to handle loss of life in a trial. The study also found that the amount of insurance cover provided by sponsors varied according to the country where the trial was being conducted, with research subjects in the West

being provided greater coverage than Indian research subjects (Thatte, Kulkarni-Munshi and Kalekar 2009).

In the year 2009, ICMR issued draft guidelines specifically regarding compensation for injury during clinical trials. The guidelines state, for example, that pregnant women who lose their unborn children have the right to demand compensation (Sinha 2011). These guidelines have not yet been formalized and in any case are not enforceable by law. While the Rules require sponsors to report the occurrence of serious adverse events the legislation does not make the sponsor liable to compensation for risks that are inherent to a trial and not always predictable at the start of the research. The only mention in the Rules of some form of injury-related protection for trial subjects is an assurance from the investigator that sufficient medical care is available (Schedule Y, amended 2005, The Drugs and Cosmetics Rules 1945).

Sponsors have often denied allegations of death or disability as a result of the trial and the onus of proving trial related injury is on the research subject or the individual's family who has no option but to rely on the good offices of the investigator, the institution and the ethics committee. On June 6, 2011, an article in the *Times of India*, reported the DCGI statement regarding greater stringency regarding holding sponsors liable for deaths and injuries that occur during clinical trials. "For the first time ever, DCGI Dr Surinder Singh" (Sinha 2011:12) summoned nine pharmaceutical companies—Wyeth, Quintiles, Lilly, Amgen, Bayer, Bristol Mayer, Snofi, PPD and Pfizer—to pay compensation to legal heirs of trial subjects who died in clinical trials in the year 2010. According to the licensing body, 25 trial subjects had died in 2010 in clinical trials conducted by these nine companies and only five families were compensated. The drug companies claimed difficulty in identifying the legal heirs of deceased as a reason for not compensating their families (Sinha 2011).

While the DCGIs clamping down on pharmaceutical companies is commendable, in the absence of legislation ensuring insurance cover and/or financial compensation for trial subjects in case of injuries, disability or death, and a means of redressal for the injured, trial subjects will continue to depend on arbitrary action taken by regulatory authorities. Comprehensive regulation on the issue of compensation for trial-related

injuries will also give IECs greater agency in performing their role of protecting the welfare of the research subject.

5. Undue inducement and professional subjects

Regarding payments offered to trial subjects for their participation in a clinical trial, both national and international guidelines hold the following position:

> Participants may be paid for the inconvenience and time spent...however, payments should not be so large or the medical services so extensive as to make prospective participants consent readily to enroll in research against their better judgment, which would then be treated as undue inducement (ICMR 2006:25).
>
> Payments in money or in kind to research subjects should not be so large as to persuade them to take undue risks or volunteer against their better judgment. Payments or rewards that undermine a person's capacity to exercise free choice invalidate consent (CIOMS 2002, Guideline 7: 46)

These statements are based on two assumptions: firstly, inducements are necessary to encourage individuals to volunteer, and to reduce difficulties in their experience of participating in research and secondly, there is a difference between inducements that are 'due' or morally acceptable, and inducements that are 'undue' or not acceptable (Macklin 1981).

It is the responsibility of the IEC to ensure that trial participants are not consenting to research due to undue inducements. Participating in research due to an excessive offer of money could influence individuals in making wrong judgments by overestimating the benefits of research and underestimating the risks involved and as a result, compromise their personal safety and welfare. Undue inducements are, however, not clearly defined in guidelines and regulations and therefore ethics committees are faced with several questions. How should the committee determine when an inducement becomes an undue inducement? What are the practical criteria, if any, to be used? Can the distinction between due and undue inducements be made objectively or are these terms rooted in subjectivity and therefore vary in definition from person to person?

Minimal guidance in regulations and guidelines in defining inducements that are ethically acceptable is a matter of concern, especially, in developing countries where

people in circumstances of impoverishment might find the offer to make quick money in clinical trials difficult to resist. Financial incentives, therefore, result in some individuals choosing to participate in several trials at a time, exposing themselves to unnecessary health risks. Professional subjects or those individuals who earn an income by continuously participating in trials are common in Phase I trials in the U.S. and also in India (Abadie 2010; Gulhati 2010). The dangers of steady exposure to drugs that can be potentially harmful are risks not considered by the professional subject. In addition, drug companies and CROs who need to recruit trial subjects as fast as possible overlook the risks that individuals who participate in multiple trials might be exposed to (Abadie 2010).

The reporting of a death in a clinical trial in Hyderabad, in the year 2008, clearly illustrates how financial incentives used to recruit people in clinical trials can expose trial subjects and their families to enormous harm amounting to disability and death. Several newspapers reported the "suspicious" death of a 24-year old man, K. Surendar as the result of his participation in a drug trial. K. Surendar was one of 50 healthy volunteers in a bioequivalence study to compare the efficacy of the drug of one company with the efficacy of the same molecule developed by another company. The trial was conducted by a CRO, GVK Biosciences, to test the drug Felodipine, approved by the DCGI and world over for controlling blood pressure. K. Surendar died after consuming the first round of the drug after he complained of chest pains. The Hyderabad police alleged that the trial subject might have been participating in multiple trials and his death could have been caused due to simultaneous exposure to several different kinds of drugs. K. Surendar's family claimed that the trial subject was being paid rupees one hundred and fifty a day for participating in the trial. The CRO refuted claims about the payment offered and stated that since K.Surendar died eight days after consuming Felodipine, the drug would have been washed out of his system in that period of time (Radhakrishna and Mudur 2008). According to Gulhati "every protocol requires that trial subjects should not be consuming other drugs" and so "why was he [K.Surendar] enrolled?" (Gulhati 2010). Gulhati further adds that the "lure of money is the reason" why K.Surendar participated in the trial. His death has being reduced to a number—GVK 068074—in the trial's records with no compensation provided to the trial subject's family for their loss. The CRO that conducted the study was in clear violation of ICMR's guidelines that explicitly state

the need for bioequivalent studies to protect the welfare of trial subjects that are usually conducted on healthy individuals: "all safeguards to protect participants must be in place, including ethical review of protocol, recruitment methods, compensation for participation, evidence of non-coercion and consent procedures. It is in such studies that volunteers often participate at short intervals and may participate at different centres within less that the prescribed period of three months between two studies. Mechanisms to prevent this must be developed at the study site" (ICMR 2006: 40). The CRO was not held accountable for the Felodipine drug trial by India's regulatory authority and there is no information available in the public domain regarding the role of an ethics committee or if any ethical review had taken place.

The ambiguity on the issue of inducements has resulted in several interpretations on the contentious subject. Ezekiel J. Emanuel and others contend that inducements become undue not because of people's unfortunate personal circumstances that coerce them into participating in a trial but "when the person's unfortunate circumstances and compromised judgment are combined with accepting a seriously unfavorable risk-benefit ratio that threatens fundamental interests" (Emanuel, Currie and Herman 2005:338). Emanuel and others also argue that concern for the issue of undue inducements, especially in the developing world, is unfounded if ethics committees are doing there job effectively because it is the responsibility of ethics committees to only approve research that is ethical and that which presents a favourable balance of risks and benefits. Therefore, even if individuals make the wrong decision, the ethics committee will not approve those clinical trials that will expose subjects to unnecessary harms. The position held by Emanuel and others of misplaced concern of undue inducements because of the protection offered by ethics committees is disapproved by Schonfeld *et al* who argue that ethics committees cannot be made entirely responsible for ensuring that a payment made is not an undue inducement because the potential trial subject will have his or her own definition of risks and benefits of the proposed research. Although monetary payments are not considered as benefits of a research study, the potential trial subject is likely to define risk and benefit on the basis of the payment offered and not perhaps on how an ethics committee or investigator will assess risks and benefits of research. By neglecting an individual's perception of factors that motivate him or her to agree to participate in a trial is neglecting the individual's right to autonomy and the "subjective nature of

value makes it impossible for IRBs to anticipate whether or not a payment will serve as an undue inducement for participation in all cases" (Schonfeld 2005:23). Therefore there can be no fixed payment below which it can be defined as due and above which it is defined as an undue payment because the value that one person attaches to a sum of money will be different to that of another person (Macklin 1981). If payments are kept low to err on the side of caution, the research may result in violating the ethical principle of distributive justice because people who are likely to participate for low compensation will be those from economically disadvantaged backgrounds (Macklin 1981). According to R. Macklin, the solution, therefore for ethics committees to ensure that individual consent to research is not an outcome of coercion and undue inducement is to be aware of the methods used by investigators to select trial subjects for each research protocol and the amount of payment being offered to each individual (Macklin 1981).

The CIOMS guidelines also acknowledge the lack of guidance for ethics committees on the subject of undue inducement and the difficulty in differentiating between payment that is suitable and inducement that is not acceptable: "An unemployed person or a student may view promised recompense differently from an employed person. Someone without access to medical care may or may not be unduly influenced to participate in research simply to receive such care" (CIOMS 2002, Guideline 7: 46). The best option, therefore for ethics committees according to the CIOMS guidelines is to evaluate monetary and other kinds of incentives "in the light of the traditions of the particular culture and population in which they are offered, to determine whether they constitute undue influence. The ethical review committee will ordinarily be the best judge of what constitutes reasonable material recompense in particular circumstances" (CIOMS 2002, Guideline 7:46). The ethics committees must however be caution against the excessive use of cultural relativism, which could cause more harm to trial subjects in the developing world than good (Petryna 2005). A study conducted by Thatte and others on the issue of insurance for research related injury (discussed earlier in this chapter) found that patients in Indian trials were insured for amounts much less than patients in trials in the U.S. for research related injures. A difference in living standards between the two countries was the explanation offered by sponsors for differential payment (Thatte, Kulkarni-Munshi and Kalekar 2009).

6. Standard of care during and after a clinical trial

In research protocols reviewed by the IEC, the investigator is required to explain the standard of care that will be used in the trial and also justify the use of a placebo arm, if any, in the trial. Central to the argument on the issue of the kind of care provided is the contested definition of the term 'standard of care'. Does standard of care imply a universal standard of care or the best current treatment available that should be made accessible to trial participants the world over or does it refer to the best option for treatment that is locally available in the region where the trial is being conducted? The debate on the ethical standard of care has its roots in the HIV trials of Africa. These HIV trials denied women participants the known effective treatment or standard of care that can reduce incidence of perinatal infection by two-thirds or could save the lives of one of seven new born babies born to women infected with HIV (Lurie and Wolfe 1997). Proponents of the HIV trials defended the use of a placebo by explaining that the standard regimen was not feasible to use in the African continent because of dysfunctional public health systems that would not be able to afford the standard of care and nor would they be able to support early counseling and monitoring services for women that are essential for taking the intensive and lengthy standard regimen. Therefore, proponents of the placebo argue that a cheaper and easier treatment regimen is the better and more practical option rather than the standard of care used in the West. While critics of the HIV trials like Lurie and Wolfe support the need for cheaper and effective treatments in both the developing and western world, they argue that the study design was unethical and would not have been acceptable in the U.S, and therefore the justification used amounted to ' "ethical relativism" ' (Vastag 2000: 2984). In the context of the HIV trials, the standard of care refers to non-universal standard of care or local treatment, which could mean no treatment at all in several countries of the developing world, also suggesting that economic priorities override ethical scientific standards in the planning of research design in clinical trials (Tangwa 2004). Placebo-controlled trials for effective results is not the only option, state the critics, who believe that equivalency trials comparing the standard of care with shorter Zidovudine regimens could have been conducted preventing the deaths of hundreds of children (Lurie and Wolfe 1997). Harold Varmus and David Satcher from the National Institutes of Health disagree. They state that while a placebo-controlled trial is not the only option for investigators to study an

intervention, an equivalency trial will not necessarily provide the answers whether the interventions used are better than nothing:

> The most compelling reason to use a placebo controlled study is that it provides definitive answers to questions about the safety and value of an intervention in the setting in which the study is performed, and these answers are the point of the research. Without clear and firm answers to whether and if so, how well an intervention works, it is impossible for a country to make a sound judgment about the appropriateness and financial feasibility of providing the intervention (Varmus and Satcher 1997:1004).

Varmus and Satcher reject the criticisms of the HIV trials being unethical. They argue that women in the developed world were not always allowed to use their right to autonomy to participate in clinical trials and, as a result, they were deprived of the benefits of clinical research. They explain the difficulty in applying ethical principles of Respect for Persons, Beneficence and Justice, because of their conflicting nature. Varmus and Satcher ask how to apply ethical principles to research conducted in the developing world and state that people in these countries also deserve access to research that serves the health needs of their country. Treatment available in the U.S. might not be possible in another country because of high costs or inadequate health care systems:

> Might we support a trial in another country that would not be offered in the United States? Yes, because the burden of disease might make such a study more compelling in that country. Even if there were some risks associated with intervention, such a trial might pass the test of beneficence. Might we elect not to support a trial of an intervention that was beyond the reach of the citizens of the other country? Yes, because that trial would not pass the test of justice (Varmus and Satcher 1997:1003-1004).

Richard Cash, a senior lecturer at the Harvard School of Public Health, argues that sometimes, secondary care is not secondary and products that are highly priced should not be tested on people who cannot afford them. Cash argues that while a universal standard of care during the trial and post-trial access to beneficial outcomes is a fair and reasonable idea it is not always appropriate in a low-resource setting. Cash believes that there are problems in implementing post-trial access especially if a drug is in the process of approval or because of difficulties in the monitoring of side effects (Cash 2010). Cash's argument against post-trial access refers to the practical and logistical problems of implementation and cannot be the reason for justifying the denial of a beneficial treatment to the research subject after the trial is over.

The Declaration of Helsinki stated that post-trial access should be ensured by ethics committees who should review protocols for provisions made to provide trial subjects the effective drug or intervention following the trial (Wolinsky 2006). The practical application of this guideline has however not been resolved as questions regarding who will pay, how patient access to beneficial drug will be assured and by whom, after the trial is over, remain unanswered and the issue continues to be debated.

7. Conflict of interest

In order to recruit large numbers of trial subjects as quickly as possible, pharmaceutical companies or CROs induce doctors into the subject recruitment process by offering cash payments and other incentives such as foreign travel ostensibly for educational purposes (Angell 2004; Gulhati 2011). In the year 2000, in the U.S, a report issued by the HHS, Office of Inspector General, stated that doctor's in one trial were paid 12,000 dollars for each patient enrolled, with a bonus of 30,000 dollars on the recruitment of the sixth patient (Angell 2004:30-31). In India, too, "income from clinical trials has become by far the largest single source of revenue" for both government doctors and those in private practice (Gulhati 2011:4). In May 2011, an editorial in the *Monthly Index of Medical Specialties* and a month later an article in the *Times of India* revealed the large sums of money paid to several doctors to recruit subjects for clinical trials conducted in public hospitals in Madhya Pradesh. Investigations indicated that between the years 2005 to 2010, a total of 2,365 patients were recruited for clinical trials to be conducted in five government medical colleges, of which, 1,521 subjects, including 1,170 children, were recruited by just six investigators from one institution–M.G.M Medical College and the associated M.Y Hospital in the city of Indore (Gulhati 2011:4; Nagarajan 2011:17). A report on the illegal trials by the Government's Economic Offences Wing stated that during 2006 to 2010 the six doctors conducted 76 trials and 81 deaths have been reported (Singh 2011:7). An RTI application revealed details of the amounts paid to doctors from the M.G.M Medical College. For example, Dr. Hemant Jain from the paediatrics department received rupees 56 lakhs, Dr. Ashok Bajpai, a professor of medicine made 41.37 lakhs and Dr. Anil Bharani, a professor of cardiology received rupees 44 lakhs. The average monthly salary of rupees 75,000 for senior professors at the medical college stands in sorry contrast to the large sums of money made by the doctors from the clinical trials. Investigations also revealed that a Clinical Trial Agreement with a

doctor from the same medical college—who was paid 26,000 rupees per patient—and the CRO, Quintiles India who was representing the drug company, Alcon, stated that the doctor's payment should be sent directly to her personal account. In response to the RTI application, the M.G.M Medical College and M.Y Hospital admitted that the institution had not received any financial payments for the trials. In addition to information on financial inducements to doctors conducting the clinical trials, it was also revealed that the trials were not approved by the IEC of the M.G.M Medical College but ethical approval was sought from independent ethics committees located outside the state of Madhya Pradesh (Gulhati 2011: 4; Nagarajan 2011:17).

The doctors of the M.G. M Medical College clearly violated the ethical obligation of the physician-investigator who is directly involved with the clinical trial to reveal any conflict of interest. While revealing a conflict of interest is good clinical practice its admission depends on the integrity of the investigator. It is an issue that is often forgotten by ethics committees in light of other ethical concerns but a conflict of interest can pose a major risk to trial subjects as large scale financial payments can induce doctors' into recruiting the wrong or ineligible patient for the trial (Angell 2004).

8. Application of the fundamental ethical principles

The application of the three fundamental ethical principles in clinical research articulated in the Belmont Report is also known as Principlism–the most widely used approach in biomedical ethics popularised by T. L Beauchamp and J.F Childress. The Principlism approach that defines ethical principles as "universally valid norms that warrant us in making inter-cultural and cross-cultural judgements about moral depravity, morally misguided beliefs, savage cruelty, and other moral failures" can be complicated to apply in the ground realities of clinical research (Beauchamp 2003:269).

Charles L. Bosk argues that Principlism works on the assumption that the ethical principles provide a single, quick fix solution to every ethical problem, which function independently of "person, place, or time" (Bosk 1999:62) Bosk urges the proponents of principlism to be aware of the different contexts in which research is conducted and that ethical principles are "attached to persons" who have their own history and culture and also interests. Using the example of the unequal doctor-patient

equation, Bosk states that applying ethical principles to change the "inappropriate values" that characterize the doctor-patient relationship will not resolve the problem of the power dynamics and the structural arrangements, that underlie the relationship and which in fact may discourage individuals to actually exercise the right of independent decision-making that has been granted to them by the ethical principles (Bosk 1999: 54-63).

Macklin believes in the soundness of the ethical principle approach but says that it needs to be constantly re-evaluated and examined (Macklin 2003). He uses an example of a Jehovah's Witness case to illustrate his point (Macklin 2003). He states that if a capable adult refuses blood transfusion because it is against the tenets of his religion, then what are the options available to the physician in-charge. The physician can respect the patient's right to autonomy and accept the patient's decision of refusing treatment even if it puts the patient's life in danger or the physician can exercise the principle of Beneficence and administer the treatment so that harm is minimized. If this is the level of analysis that Principlism can offer to a physician or a physician-investigator then it is clearly states that the principles can provide no solutions. However, proponents of Principlism state that the ethical principles do not in fact provide ways of choosing or making deductive conclusions on the basis of rules but that "moral agents" have to arrive at their own conclusions using the "common moral commitments" provided by the ethical principles (Macklin 2003:275). Macklin however asks if Principlism has the answers to the dilemma of balancing the risks and benefits of research in the case of the Jehovah's Witness. For the Jehovah's Witness harm from accepting the blood transfusion, which means being denied eternal redemption, is much greater than the harm incurred by refusing the blood transfusion. If the Jehovah's Witness has a family to support then accepting his autonomous decision can put the family in danger and the principle of Respect for Persons and Respect for Beneficence are in conflict with each other and the physician is faced with the dilemma of which ethical principle to prioritize. Macklin, therefore questions, the scope of the principle of Beneficence and if the investigator also has the moral obligation to not harm others, apart from the individual patient.

Macklin uses the example of the Jehovah's Witness case as a reminder that the application of the fundamental ethical principles is complex. The Institutional Ethics

Committee who is the upholder of the ethical principles must be aware of these complexities and that the ethical approach of Principlism requires a constant analysis of the context in which it is applied (Macklin 2003).

Conclusion

From the discussion in this chapter it is apparent that the role of an ethics committee is complex and multifarious. Members of ethics committees may encounter situations in the course of an ethical review for which there are no easy solutions. With limited guidance from guidelines on how to tackle major ethical dilemmas, ethics committee members must make decisions based on an adequate understanding of the fundamental ethical principles and their conflicting nature.

Organizations like the Forum for Ethical Review Committees in the Asian and Western Pacific Region (FERCAP) and the WHO Strategic Initiative for Developing Capacity in Ethical Review have been established for building regional and global capacity of ethics committee members and improving the standard of ethical review. The Forum for Ethics Committee Review in India—the Indian chapter of FERCAP—formed in collaboration with ICMR to create a platform for ethics committee members to share the challenges of their work and widen their understanding of ethics in clinical research is still in its nascent stages. Ethics committees in India do not have support systems and other mechanisms to ensure that they are doing their job well says, Jesani, who also expresses concern that there are no guarantees that a completed ethical review of a protocol indicates protection for the trial subject.

Chapter 4

The Inner Workings of an Institutional Ethics Committee: An Analysis of the Study's Findings

Introduction

Seventeen members of Institutional Ethics Committees, representing five hospitals in Delhi, were interviewed between the months of November 2010 and April 2011. Of the five hospitals, two are public institutions, two are private institutions and one is a trust hospital. To ensure anonymity, the hospitals are being referred to as Public Hospital A, Public Hospital B, Trust Hospital C, Private Hospital D and Private Hospital E. The processes involved in data collection and the findings of the study will be the focus of this chapter. The discussion and analysis of the data is organized on the basis of different themes for greater clarity and deeper understanding of the findings. The themes used are not mutually exclusive of each other and each topic or theme must be read in relation to the other.

1. Contacting IEC members

In three Hospitals: Public Hospital A, Public Hospital B and Trust Hospital C, the first IEC members to be contacted were the Member Secretaries. In Private Hospital D, initial contact was made with the Chief of Medical Excellence Programmes who is also a member of the IEC. In Private Hospital E initial contact was made with an IEC member not affiliated with the institution. Member Secretaries of the IECs of Public Hospitals A and B were identified through the institution's website and through an Internet search respectively. The Member Secretary of the IEC of Hospital C and the Chief of Medical Excellence Programmes of Private Hospital D were identified through the researchers personal contacts. The non-affiliated member of Hospital E was identified through the researcher's supervisor.

At Public Hospital A and Private Hospital D, contact details—email addresses, telephone numbers and designations—of IEC members were made available to the researcher by the Member Secretary and the Manager of Clinical Research respectively. Members with an email address were contacted by an email briefly explaining the purpose of the study and also requesting an appointment. The email was followed by a telephone call. Other members were contacted by telephone and

where communication was not possible by either telephone or email the researcher made contact by visiting the member or the member's personal assistant at the member's place of work.

2. Profile of medical institutions

Public Hospital A, established in the late 1950s, is one of India's premier, public, tertiary-care institutions that also offers super-speciality facilities. It is a medical college that provides both undergraduate and postgraduate medical education. Public Hospital B, one of Delhi's oldest medical hospitals—established under colonial rule—is a public, tertiary care institution that offers a postgraduate medical education programme. Trust Hospital C, another old and reputed medical institution, is a tertiary care hospital whose board of management is governed by a trust. The hospital provides training for postgraduate and postdoctoral medical students as well as grants post doctorate fellowships. Private Hospital D is a relatively new hospital that functions under the umbrella of a larger business corporation, established in the 1980s. It is a tertiary care institution as well as a multi-speciality hospital. Private Hospital D also has an educational institute that provides training programmes for doctors, nurses and paramedics. Private Hospital E, established in the 1980s, is a dedicated tertiary facility for cardiac related care and is part of a larger network of hospitals providing cardiovascular services in different parts of the country.

3. Profile of participants

In keeping with India's ethical guidelines and regulations for ethics committee membership the IEC members interviewed across the five institutions represented a combination of men and women with medical/scientific and non-medical/non-scientific backgrounds.

Of the 17 IEC members interviewed, nine members were affiliated to their respective hospitals while eight members were not. Of the total number of interviewees, nine were men and eight were women members. Of the nine affiliated members six were women and of the eight non-affiliated members two were women.

The nine affiliated members were clinicians or basic scientists who occupied senior positions in their respective hospitals. Seven of them were departmental heads in their respective institutions, in the fields of: Anatomy, Cytopathology, Clinical and

Laboratory medicine, Laboratory Medicine, Transfusion Services and Haematology and Medical Excellence. The Member Secretaries of public Hospital A and Trust Hospital C were both department chairs and the Member Secretary of Public Hospital B was a senior doctor at the hospital. The other two affiliated members interviewed were a professor of pharmacology and an editor of a prestigious medical journal.

Of the eight non-affiliated members, six individuals had non-scientific/non-medical backgrounds. The six non-scientist/non-medical members interviewed were: two practicing Supreme Court lawyers, one of whom is a retired High Court judge; one Hindi language specialist who is described as a lay person, one senior employee of a global television channel and two social scientists. The non-affiliated members with medical backgrounds included a clinical psychologist who has her own private practice and a former departmental head of Pharmacology.

4. Constitution of an IEC

Regulations on IEC membership require a multi-disciplinary approach for the care and protection of human subjects in clinical research. Ethical review of a research protocol needs to be guided by a combination of viewpoints so that the ethical conduct of both the technical and non-technical aspects of research can be assessed. To ensure a multi-disciplinary ethics committee, individuals with medical and scientific expertise and those who represent the legal profession, the social and behavioural sciences, the field of ethics or moral philosophy and community representatives should be appointed to the ethics committee. All IEC members should not be affiliated to the institution and some members including the Chairperson should be selected from outside the institution to ensure autonomy in ethical review and to prevent decisions being made with a pro-institution or pro-sponsor bias. Membership of an IEC therefore falls into three categories: clinicians/basic medical scientists who are affiliated or employees of the institution; members who are not affiliated to the institution but can also have a medical occupation; members who are not affiliated to the institution and do not have a medical/scientific background such as lawyers, social scientists and psychologists.

Although "the two hallmarks of an IEC" are "independence" and "competence", according to the ICMR guidelines (ICMR 2006: 9), the degree of autonomy available to IEC members in proposal review and decision-making has been questioned. Amar

Jesani questions the true independence of an IEC when the responsibility of appointing the ethics committee lies with its institution and not an external body. Jesani asks why an ethics committee cannot be funded by a public authority separate from the institution to ensure the autonomy of ethics committees and the greater possibility of genuine oversight (Jesani 2010). Edgar and Rothman also question the independence of ethics committees in the U.S. when the responsibility of appointing the members of a monitoring committee is given to the "leadership of an institution, which by its very nature cannot survive without the funds and fame brought in by clinical research..." (Edgar and Rothman 1995: 490).

Findings:

a) All IECs were appointed by institutional/operational heads.

b) Membership to all IECs was multidisciplinary with a mix of affiliated and non-affiliated members.

c) All IECs had Chairpersons who were external to the institution and Member Secretaries who are employees of the institution.

d) The initial appointment term for members of three IECs is two to three years, with the exception of Private Hospital E.

e) The dominant voice of an IEC belongs to members who are associated with the institution.

a) All IECs were appointed by institutional/operational heads

In accordance with ICMR guidelines, all five IECs of the study were constituted by the senior rung of their respective institutions: The IEC of Public Hospital A is constituted by the hospital's chairperson, the IEC of Public Hospital B is constituted by the Medical Superintendent, the IEC of Trust Hospital C is appointed by the board of members, the formation of the IEC of Private Hospital D is determined by the institutional head, according to the SOP, and in the case of the IEC of Private Hospital E, the draft SOP—according to the non-affiliated member—states that the Dean of Research and hospital administration will recommend appointments to the IEC.

b) Membership to all IECs was multidisciplinary with a mix of affiliated and non-affiliated members

All IECs were organized on the basis of ICMR guidelines with each IEC comprising members from various professions—clinicians, basic scientists, lawyers, social and

behavioural scientists and ethicists (see Table: IV.1). On average, half the members of IECs were from within the hospital and half were from outside, with the exception of Private Hospital E that had only one member—the Member Secretary—affiliated to the institution.

Regarding gender distribution, the information available on three committees indicates that each IEC had about three to four women members. The women members included both affiliated (medical) and non-affiliated/non-scientist members.

Table IV.1 Composition and Membership of Institutional Ethics Committees

	HOSPITAL A		HOSPITAL B		HOSPITAL C		HOSPITAL D		HOSPITAL E	
Type	Public		Public		Trust		Private		Private	
Number of Members	15		11		13 Approximately		15		10 Approximately	
Affiliated Scientist Members	8		6		7 or 8		7		1	
Composition of Affiliated Scientist Members	**Role on IEC**	**Title & Dept.**	**Role on IEC**	**Title & Dept.**	**Role on IEC**	**Title & Dept.**	**Role on IEC**	**Title & Dept.**	**Role on IEC**	**Title & Dept.**
	1. Basic Scientist 2. Basic Scientist 3. Clinical Scientist 4. Clinical Scientist 5. Clinical Scientist 6.Pharmacol-ogist 7. Clinical Scientist 8. Member Secretary	Head, Dept. Anatomy Head, Dept. Pharmacology Prof. Medicine Editor Medical Journal Prof. I/C Emergency Medicine Prof. Pharmacology Asst. Prof ENT Head, Haemotology	Data Unavailable	Senior Paediatrician Asst. Prof. Paediatric Surgery Consultant in Medicine Sr. Pathologist Labour Welfare Psychiatric Social Worker	1. Member Secretary Further Data Unavailable	Head, Dept. of Cytopathology Further Data Unavailable	1. Member Secretary 2. Clinical Scientist 3. Clinical Scientist 4. Clinical Scientist 5. Clinical Scientist 6. Clinical Scientist 7. Clinical Scientist	Administrator, Medical Services Chief, Medical Excellence Programme Sr. Consultant, Cardiology Chair, Anaesthesiology Director, Nuclear Medicine Director, Anatomical/ Surgical Pathology Director, Lab. Medicine	1. Member Secretary Further Data Unavailable	Further Data Unavailable
Non Affiliated Scientist Members	4		4		2-3 Approximately		2		Data Unavailable	

	HOSPITAL A		HOSPITAL B		HOSPITAL C		HOSPITAL D		HOSPITAL E	
Composition of Non Affiliated Scientist Members	**Role**	**Title**	**Role**	**Title**	**Role**	**Title**	**Role**	**Title**	**Role**	**Title**
	1. Chair	Ex-Prof. of Medicine, Hospital A	1. Basic Scientist	ICMR	Data Unavailable	Data Unavailable	1. Chair	Dean, Medical College	Data Unavailable	Data Unavailable
	2. Ethicist	Sr. Scientist, ICMR	2. Pharmacol-ogist	Head Dept. of Pharmacology			2. Pharmacolo-gist	Ex Head, Dept. Pharmacology, Hospital A		
	3. Clinical Scientist	Ex Head Dept. of Obs/Gyn, Hospital A	3. Pharmacol-ogist	Associate Prof. Pharmacology						
	4. Clinical Scientist	Ex-Chief, CDER, Hosp. A	4. Clinical Scientist	Associate Prof. Physiology						
Non-Affiliated Non Scientist Members	3		1		2 Approximately, there may be more		6			
Composition of Non-Affiliated Non Scientist Members	**Role**	**Title**	**Role**	**Title**	**Role**	**Title**	**Role**	**Title**	**Role**	**Title**
	1. Legal	Ret. Justice, High Court	1. Legal	NHRC	1. Legal	Data Unavailable	1. Legal	Advocate, Supreme Court	1. Social Scientist	Data Unavailable
	2. Social Scientist	Prof. Indian Inst. of Public Administration	Further Data Unavailable	Further Data Unavailable	2. Social Scientist		2. Legal	Advocate, Supreme Court	2. Legal	
	3. Lay	Ex-Chair Dept. of Indian Languages, JNU					3. Social Scientist	MD, Electronic Media	3. Lay	
							4. Lay	Social Worker		
							5. Social Scientist	Clinical Psychologist		
							6. Legal/Social Scientist	NHRC		

c) All IECs had chairpersons who were external to the institution and member secretaries who are employees of the institution.

Every IEC has a Chairperson who is not affiliated to the institution and a Member Secretary who is an employee of the institution—both membership requirements stated in ICMR guidelines.

d) The appointment term for members of three IECs is two to three years, with the exception of Private Hospital E

The appointment term for members of IECs of Public Hospitals A and B, and Private Hospital D is based on ICMR guidelines that recommend each member to be initially appointed for a period of two to three years, at the end of which the committee will be reconstituted with half of the members being replaced (ICMR n.d.). Among the three SOPs available to the researcher, only the SOP of Private Hospital D stated the terms of appointment for IEC members.

According to a non-affiliated/non-scientist member of the IEC of Private Hospital E, the membership term is four years that can be extended twice for a period of two years each time. The member however stated that his letter of appointment did not mention any tenure.

e) The dominant voice of an IEC represents members who are associated with the institution.

All IECs in this study fulfilled ICMRs criteria for a competent and an independent ethical review by appointing a multidisciplinary team and selecting a Chairperson from outside the institution. However, the most assertive voices of the IECs are the clinicians/scientists who are usually affiliated members of the institution and the ones who dominate the decision making process. The findings, particularly of Public Hospital A and Private Hospital D indicate that there is always a danger that institutional interests will take precedence over the trial subject when the stronger force on the committee has an affiliation.

Public Hospital A

The findings from Public Hospital A indicate that the Chairperson of the IEC, although independent of the institution, is a retired Professor of Medicine of the hospital. The memorandum of Hospital A on the re-constitution of its ethics committee in the year 2008, states that an "eminent medical scientist" who is a retired

faculty member should be appointed as Chairperson of the institutes ethics committee. This considered decision of Public Hospital A to appoint a former doctor of the hospital as the head of its IEC, appears to be either a misinterpretation of the imperative for an autonomous ethics committee or a disregard for a decision making process that should be free from institutional bias. In addition to the Chairperson, two other non-affiliated members of the IEC of Public Hospital A are former, senior employees of the hospital. Therefore, from among a total of 15 members of the IEC of Public Hospital A, 11 members have some form of allegiance to the institute with eight being current employees of the institution. Current and former employees with several years of association with an institute are more likely to have allegiance to the institute's agendas and policies rather than individuals who are not associated with the institute.

Private Hospital D

The likelihood that affiliated members will protect the institution rather than prioritize the trial subject while reviewing protocols was evident during the deliberations of an ethics committee meeting of Private Hospital D where investigators—who also belonged to the institution—were presenting their research protocols. An affiliated member of the IEC who is a senior cardiologist, in response to an investigator proposing the use of a placebo arm in the proposed trial, advised the investigator to practice caution in his use of a placebo when an established treatment is known. The doctor expressed concern on placebo use because "in our hospital we have patients who are paying for everything – in public hospitals it is different. We have to protect ourselves" (Attended IEC meeting on 15.11.2010). The patient demographic of an expensive corporate hospital like Hospital D is more likely to include educated and aware patients who have greater agency to question or challenge the use of a particular therapy or treatment, and more significantly, hold the hospital liable for any wrongdoing. "Educated patients are harder to recruit" and "if something goes wrong they can say we were just asked to sign the [consent form] and not explained anything properly", said another affiliated member on the IEC (Personal interview on 6.12.2010).

The reasons cited by the IEC member for reconsidering the use of a placebo was therefore not about the potential health risk to a clinical trial subject, or even the moral dilemma that using a placebo raises, but rather to ensure that the hospital is

protected from any liability that it may have to trial subjects who can potentially challenge the approval of an IEC on the use of a placebo.

> A more serious patient can get into the placebo while ordinarily he would have been treated. There can be functional loss. He can lose a limb and take you to court. What's your safeguard? We are a private hospital (Attended IEC meeting on 15.11.2010).

In this instance, protection of the clinical trial subject was only a by-product of the institution's need to first protect its self.

While affiliated members may be inclined to prioritise institutional interests rather than ethical concerns of a protocol review, non-affiliated members may also lose sight of the IEC's primary role of protecting the welfare and rights of the clinical trial subject. At the same committee meeting of Private Hospital D attended by the researcher, another discussion centred on a multi-centre trial that had 30 sites across India, with Private Hospital D being one of the sites. From each site the sponsor of the trial required recruitment of 15 trial subjects. A non-affiliated member, with a medical background, was concerned about the proposed target of a small number of patients since small numbers can undermine the statistical significance or the research outcome of a clinical trial. The member proposed that the number of subjects in the trial should be increased to at least 40 to 50 patients and the institution should not accept the small number of 15 patients. It is the "trick of the sponsor" the IEC member stated to only recruit limited numbers from each site and it would be beneficial to the hospital if the number of patients were increased so that the trial will at least be able to arrive at an acceptable conclusion. He further stated the need for a policy decision regarding the suitable number of participants recruited for a clinical trial (Attended IEC meeting on 15.11.2010).

While the non-affiliated member's suggestion to increase the number of subjects in the clinical trial in order to produce statistically significant results and ensure scientific integrity of the research was not erroneous, increasing the number of subjects in a trial would mean putting more individuals at risk–as risk is inherent to every clinical trial. The discussion, thus, on the particular protocol centred on challenging the sponsor's requirement for subject recruitment for the sake of the

hospital's repute rather than focusing on ethical issues of the proposed project (Attended IEC meeting on 15.11.2010).

Other IECs in the study

Similar to the IECs of Public Hospital A and Private Hospital D, about half the members of other IECs in the study were current employees of the institution. The strong presence of affiliated members on an IEC begs the question: how independent are these ethics committees and does ethical review of a protocol serve institutional interests rather than the welfare of trial subjects?

It can be argued that there is also a significant presence of non-affiliated members on the IECs. For example, eight out of 15 members of the IEC of Private Hospital D are not affiliated to the institution. Since the primary objective of non-affiliated members, particularly the non-affiliated/non-medical members is to humanize a technical research protocol and represent the layman's perspective, these members could challenge biased or problematic comments made by clinicians or scientists on the team. However, the reality of ethics committee discussions indicates that the disputing of a medical expert's opinion by a non-technical ethics committee member is a rarity in the deliberations of an ethics committee meeting.

5. Selection process to an IEC

While both ethical guidelines and the legislation governing IECs stress the need for a multidisciplinary committee there are no regulatory controls or guidelines on how institutions should select their ethics committee members, and the kind of criteria that should be used to appoint, terminate or reappoint members to an ethics committee (Edgar and Rothman 1995). Research on ethics committees indicates that institutions face difficulties in identifying individuals who have both the time and necessary qualifications to attend ethics committee meetings and effectively carry out their roles (United States Department of Health and Human Services 1998 b and 1998 c cited in Anderson 2006). Institutions may therefore use the easier option of selecting members who are amenable to the rest of the committee (McNeill 1993 cited in Anderson 2006). Raymond De Vries and Carl P.Forsberg based on their study on the composition of ethics committees in the U.S in 2001 stated that:

> It is sociologically noteworthy that despite wide agreement on the need for this structured protection of patients' and research subjects' interests, there is

> little guidance or consensus on how these committees should be organized or constituted. Given concern with the protection of clients, many of whom are disadvantaged vis a vis the power and knowledge of professionals, one would expect guidelines on how to ensure their interests are represented. In fact, the haphazard organization of ethics committees is increasingly recognized as problematic (De Vries and Forsberg 2002:252).

Findings:

a) The process of identifying and selecting non-affiliated members is arbitrary.

b) When asked why they thought they had been appointed to IECs, responses from non-affiliated members included meeting the criteria for IECs to appoint outside members and because they were experts in their own fields.

c) The need to ensure ethical conduct of clinical research or an interest in ethics was not the reason why the majority of non-affiliated members joined an IEC.

d) Affiliated members did not join the IEC of their free will but were instructed to do so by the institution.

a) The process of identifying and selecting non-affiliated members is arbitrary

Interestingly the observations of De Vries and Forsberg regarding the arbitrary organization of American ethics committees is also indicated in the ad hoc methods used to appoint members to three—Public Hospital A, Private Hospitals D and E—of the five IECs in this study. Information on the selection of non-affiliated members of Public Hospital B and Trust Hospital C are not available to the researcher and therefore not discussed.

None of the three SOPs—of Public Hospitals A and B and Private Hospital D—indicate any selection criteria for appointing either affiliated or non-affiliated members. The SOP of Hospital D states that the operational head will constitute the IEC, the only reference made about the formation of the IEC, of the three SOPs available to the researcher. There appears to be neither a written policy on member selection to IECs, nor any tacit understanding either of a transparent and streamlined process for appointing members from outside the institution. Instead, non-affiliated members are appointed to the committee through word of mouth referrals in order to fulfil the criteria of a multi-disciplinary team. They are not selected because of any active volunteerism on their part to ensure the ethical conduct of clinical research or because of their previous work or experience in the area of ethics or their

understanding on the subject of human subject protection. "While many of these outsiders may understand and appreciate the scientific or ethical dimensions of research, there is no way to ensure that they are anything other than a friend of a trustee, looking for an opportunity to participate in an institutional activity (Edgar and Rothman 1995).

A non-affiliated member, from the IEC of Public Hospital A, who is a Hindi language specialist defined as 'lay person' on the team, was unsure of why the hospital approached him for IEC membership. "They must have heard about me", he said (Personal interview on 30.11.2010). Another non-affiliated member from the IEC of public Hospital A, the legal representative on the team was also unclear about the selection process. "I don't know the director appointed me. He perhaps knows me" (Personal interview on 16.12.2010). A non-affiliated member of Hospital D, a clinical psychologist with a private practice, became a member of the hospital's IEC because she is an acquaintance of a senior doctor on the committee. A non-affiliated member of Private Hospital E, who is ascribed the role of a social scientist on the IEC, became a member of the committee because of an informal recommendation by his cardiac surgeon who is a doctor in the hospital. This non-affiliate member explained the randomness of member selection to IEC being the result of the requirement of selecting one representative from each of the essential categories: "what will they do but appoint somebody that they know" (Personal interview on 6.4.2010).

The arbitrariness in selecting non-affiliated members to IECs—primarily through an informal network of professional contacts and affiliations—was corroborated by the Chief-Medical Excellence Programmes, of Private Hospital D, an affiliate member of the hospital's IEC, who was in-charge of appointing members to the committee. She explains: "members are selected through the network of experts–by word of mouth. We found out who the experts are in the industry" (Personal interview on 10.11.2010). A non-affiliated member, with a medical background, on the IEC of Private Hospital D substantiated the statement. He was the former head of the pharmacology department of Public Hospital A when he was appointed to the IEC of Private Hospital D. This non-affiliated doctor on the IEC explained that "those people who are professionally proven" with "experience in clinical research" and are senior members of reputable institutions are suitable candidates for IECs (Personal interview

on 7.12.2010). These individuals who might be proficient in their particular profession, may, however, have little or no experience in conducting an ethical review of clinical research or the expertise to confront ethical dilemmas that may arise at the start of the research, in the course of it and after the research is over.

b) When asked why they thought they had been appointed to IECs, responses from non-affiliated members included meeting the criteria for IECs to appoint outside members and because they were experts in their own fields.

The reasons perceived by non-affiliated members for their selection to IECs can be divided into two categories: the need to fulfil a multi-disciplinary membership criteria for IECs and institutional preference to appoint individuals who have achieved a degree of excellence and seniority in their respective fields.

"I guess the IRB [IEC] needed a mix of people", said a non-affiliated member of Private Hospital D—a senior employee of a global television channel—in response to why he was selected (Personal interview on 9.12.2010). According to a non-affiliated lawyer on the IEC of Public Hospital A, he was appointed on the ethics committee because "they [the IEC] have some membership requirements" (Personal interview on 16.12.2010). A non-affiliated member, who is a Hindi language specialist, on the IEC of Public Hospital A speculates that his appointment to the IEC was specifically for the task of translating informed consent forms into Hindi. The clinical psychologist, on the IEC of Private Hospital D, explains that "ethics committees look for practitioners who have excelled" and that is why she was appointed to the ethics committee (Personal interview on 2.12.2010).

c) The need to ensure ethical conduct of ethical research was not the reason why majority of non-affiliated members joined an IEC

The clinical psychologist on the IEC of Public Hospital D said it was a "big honour to be a part of an elite group of doctors" (Personal interview on 2.12.2010). At the other end of the spectrum, a Supreme Court lawyer who is non-affiliated member of the IEC of Public Hospital A, expressed his wish to resign from the committee because of his irregular attendance of ethics committee meetings: "I actually wanted to resign. They have meetings on Monday's and it is difficult to attend as I am in court" (Personal interview on 16.12.2010).

The majority of non-affiliated members did not specifically mention the import of applying ethical principles in clinical research or the significance of ethical regulation of clinical trials in India or an interest in ethics as their personal reasons for becoming members of an IEC.

Only one non-affiliated and non-medical/scientific member of the IEC of Private Hospital E, expressed the importance of regulating clinical research that is dictated by commercial interests of multinational companies:

> I don't like transnational corporations. But they are there and you have to deal with them...must have a workable position on it (Personal interview on 6.4.2011).

d) Affiliated members did not join the IEC of their free will but were instructed to do so by the institution

From the responses of affiliated members across IECs it was clear that clinicians and basic medical scientists did not join the IEC of their own volition but were instructed to do so by senior management of their respective institutions. Reponses from affiliated members to the question of why they became IEC members included: "I am doing my duty", "I joined because it was part of my job", "I didn't ask for it", "I didn't have a choice" and "I was not asked if I would like to become a member or if I was willing" can be interpreted as a decision imposed on the affiliated members by institutional authorities rather than one that has been individually motivated. As mentioned in the section on the profile of participants, several affiliated members are departmental heads or senior doctors who are overwhelmed by other professional responsibilities and commitments. Appointment to an IEC and attending committee meetings is therefore an additional burden for affiliated members. The Member Secretary of the IEC of Public Hospital B, who is a senior pathologist at the hospital, expressed her wish to be relinquished of her duties on the IEC: "I told MS [Medical Superintendent] to change me but he doesn't want to take on the headache" of appointing another Member Secretary (Personal interview on 5.1.2011).

- **Differences and Similarities**

The selection process of non-affiliated members to IECs of Public Hospital A, and Private Hospitals D and E was arbitrary in nature and there was no obvious difference in responses between members of these three hospitals. There was however a

difference between the responses of affiliated members and non-affiliated members across hospitals. While affiliated members across all five hospitals expressed membership to the IEC as a responsibility imposed on them with some implying that IEC membership was a burdensome duty, the non-affiliated members appeared to perceive the invitation of appointment as a matter of prestige and an indication of public recognition of their level of professional experience and expertise.

6. Role and responsibilities of IEC members

The work of an IEC essentially comprises an initial ethical review of new protocols and continued review and monitoring of research that has been approved. While ensuring the ethical compliance of an investigator in the research protocol the ethics committee member must be aware, at all times, of the overarching ethical principles of Respect for Persons, Beneficence and Justice (see chapters two and three for ethical principles).

The initial process of review of research protocols includes:

- Examination of informed consent documents.
- Methods used to recruit subjects.
- Ensuring that the selection of trial subjects is equitable with special attention to safeguard vulnerable groups such as women and children and the mentally challenged.
- Ensuring a favourable balance between the risks and benefits of research.
- Payment to trial subjects for participation.
- Compensation to trial subjects for risk related injuries.
- Sponsor's position on providing access to beneficial treatment after the trial.

Continuing review of research includes the periodic assessment of reports on adverse events, changes if any, in the balance of risks and benefits of the trial and the general progress of the clinical trial. Field visits to a trial site—to prevent illegal and unethical research and investigate the reporting of an adverse event—is an additional but integral responsibility of the IEC as stated both in the ICMR guidelines and also in the 2005 amendment of the Rules.

The role and responsibilities of Institutional Ethics Committees has been a subject of considerable debate in literature on ethics committees. Committee members are

criticised for focusing vast time and resources on only the content and structure of informed consent documents. Edgar and Rothman argue that despite the time Institutional Ethics Committees in the U.S., "devote to examining the language of consent forms, they are not required to investigate whether the consent language they hammer out either is actually used on the floor or serves to educate the patient...It is rare for an IRB [IEC] to leave the confines of its committee room" (Edgar and Rothman 1995: 493) to review the methods undertaken to take informed consent from trial subjects. Angus Dawson, a senior lecturer in ethics from Keele University in the U.K., states that research ethics committees must be paternalistic in their role but should move beyond their focus on content of consent forms to ensuring that the information is actually understood by the patient (Dawson 2010). According to some critics, the purpose of informed consent originally meant to ensure a trial subject's autonomous decision in consenting to participate in a trial has now become a means for the investigators/sponsors and institutions to protect themselves from medical liability rather than to protect the human subject (Rainbow 2002). Due to this disproportionate time spent on procedural matters, ethics committee members detract from the real ethical dilemmas that are encountered in the field (Bosk and De Vries 2004). Dawson argues that ethics committees need to concern themselves with a range of values such as justice as there are other ways to protect the community and informed consent should not always take priority in ethics committee deliberations. Research can be defined as just when the benefit of research or an experiment is applicable to not only "those who are socially better off but also the least advantaged; and in particular, the research participants themselves and or the community from which they are drawn" (ICMR 2006: 6). Dawson also believes that it is in the subject's access to trial benefits where the issue of justice comes in but it is missing in the core of research ethics (Dawson 2010).

Moreover, both national and international guidelines are vague about many aspects of an IEC such as the criteria for assessing minimal risk in research, the definition of undue inducement in the recruitment process of trial subjects, the degree of compensation for different kinds of trial-related injuries and the feasibility of IECs making field visits. In addition to the ambiguity in the practical application of ethical guidelines, studies on ethics committees indicate that committee members find "the rules and regulations governing their work to be onerous and often unnecessary" (De

Vries and Forsberg 2002:199) and ethics committee members may not have the time or the wherewithal to reflect on ethical issues and concerns due to the burden of procedural and administrative demands made on them as members of an ethics committee and as employees of their respective institutions.

Findings:

a) There is clarity among IEC members regarding procedural issues, with the examination of information consent documents, risks of research and the issue of insurance policy for trial subjects being the most discussed responsibilities.

b) None of the IECs make field visits to monitor on-going clinical trials. The IEC members are of the opinion that either the sponsor or a third party should be responsible for the role of monitoring trials.

c) There was limited deliberation among members on the complexities of the practical application of IEC responsibilities and limited understanding among IEC members of the scope of applying ethical principles in safeguarding the rights and interests of human trial subjects.

a) There is clarity among IEC members regarding procedural issues, with the examination of information consent documents, the issue of insurance policy for trial subjects and risks of research being the most discussed responsibilities.

- **Informed consent documents**

Both affiliated and non-affiliated members across IECs were clear about their responsibility in examining the content and language of informed consent documents and ensuring that consent forms are actually "conveying" all the information about the trial (Personal interview on 23.12.2010) such as "what are the kind of tests being done? Are they free of cost? Is anything hidden from them [the patients]" (Personal interview on 2.12.2010). A non-affiliated member, a former clinician and member of Private Hospital D, stated that the "consent form is an important document and it should be signed by a witness. The Patient Information Sheet should include the advantages and disadvantages of the trial, type of drug or device being tested and adverse effects" (Personal interview on 7.12.2010). The Member Secretary of Public Hospital A, also said that "two impartial witnesses" should be present during the signing of the consent form (Personal interview on 4.11.2010). The Member Secretary of the Trust Hospital C also expressed the importance of examining

"consent forms very minutely to see if there are no inducements, that subjects are not charged anything, that all the investigations are free" (Personal interview on 22.2.2011). Regarding the quality of consent forms, the Member Secretary of Trust Hospital C claims that "drug companies are making good consent forms", but the consent forms of projects that are not industry-sponsored do not contain all the necessary information and therefore require closer scrutiny to check "how much time [for the trial], how many visits are required, how much blood will be taken" (Personal interview on 22.2.2011). A non-affiliated member—a Hindi language specialist—from the IEC of Public Hospital A claims that he has "a small work" on the committee. He perceives the checking of the language of consent forms as his main role on the IEC: "I check to see if the Hindi translation is correct. The patient's information should be in their language. If they are Muslims it should be in Urdu" (Personal interview on 30.11.2010).

- **The sponsor's obligation to provide insurance or compensation for trial related injuries**

Affiliated members across IECs, including the Member Secretaries of Public Hospital A and the Trust Hospital C stated the issue of having to negotiate with sponsors of clinical trials for the provision of insurance for research subjects. The Member Secretary of the IEC of Trust Hospital C checks "to see if there is a valid insurance policy" and sponsors are asked to provide "a copy of the insurance certificate" (Personal interview on 22.2.2011). The Member Secretary of the IEC of Public Hospital A stated that her institution makes insurance cover "mandatory" (Personal interview on 26.11.2010), and for projects that are not industry-sponsored and therefore, less likely to insure its trial subjects, the IEC ensures that the hospital provides insurance. Two affiliated members from the IEC of Private Hospital D clearly expressed the importance of obtaining assurances from sponsors in providing an insurance policy or monetary compensation for trial subjects in case of trial related injuries and ensuring that patients do not have to incur expenses during the trial:

> Patients should not be hurt physically or financially. They should not be spending money (Personal interview on 6.12.2010).

> We see if the patient has been insured by the sponsor. No unnecessary investigations are carried out. Patients do not have to pay for anything (Personal interview on 6.12.2010).

The Member Secretary of the IEC of Public Hospital B also expressed close vigilance of drug-company sponsors as one of her major roles: "We are very strict especially as far as the sponsors are concerned who are usually MNCs [multinational companies]" who "come to government hospitals" for recruiting "poor patients" (Personal interview on 5.1.2011). The Member Secretary was of the opinion that the sponsor should be responsible for any "insurance liability" (Personal interview on 5.1.2011). She expressed her concern about the agendas of multinational companies conducting trials in the developing world: "the insurance amounts that the MNCs keep for subjects in the West is much higher than they do here" (Personal interview on 5.1.2011).

- **Benefits of research**

Two members from the IEC of Private Hospital D—one affiliated member and one non-affiliated member—expressed the need to ensure that sponsors of clinical trials who are "pushy" drug companies who want "the work done" (Personal interview on 6.12.2010) were conducting research that was beneficial to the patient and "not for the benefit of the company" (Personal interview on 9.12.2010). If the research had no potential benefit to the patients, an affiliated member from the IEC of Private Hospital D expressed that it "should at least not do any harm" (Personal interview on 6.12.2010).

- **Risks of research**

Six members–both affiliated and non-affiliated members across IECs expressed the issue of safety in a clinical trial. Three non-affiliated members, all from the IEC of Private Hospital D specifically mentioned the importance of informing the patient about the risks associated with the trial and the likelihood of adverse events or side effects that might occur in the course of the trial. A non-affiliated member—a senior employee of a television channel—of the IEC of Private Hospital D, while acknowledging, that "tests are necessary" and "human trials are required" also said that IECs should ensure that the "known risks are identified, if information on the risks are disseminated to the IRB [IEC], to the patients and the patient's family" (Personal interview on 9. 12. 2010).

- **Justice in research**

Only the Member Secretary of Trust Hospital C mentioned the issue of justice when she was asked about the role of the IEC: "if the drug is meant for development in the

USA and will not be used in India then we don't give permission for the trial" (Personal interview on 22.2.2011).

- **Equitable selection of trial subjects**

Only one member–a non-affiliated member of the IEC of Private Hospital D alluded to the issue of the IEC's role in ensuring fair recruitment of people into clinical trials. The member said that IECs need to ensure that the drugs are tested "on the right number of patients" and "on the right patients" (Personal interview on 9.12.2010).

- **Inducements in the form of trial related expenses**

Two members–the Member Secretary of the IEC of Trust Hospital C and a non-affiliated member from Private Hospital D mentioned the need to oversee payment to trials subjects for transport costs incurred to and from the trial site. The non-affiliated member from Private Hospital D referred to ensuring that the Primary Investigator of the trial had considered the matter of transport in the consent documents. The Member Secretary of the Trust Hospital C explained that the hospital provides the transport related payment to trial subjects: " Each patient is given rupees 500 per visit. If they are from outside Delhi then the amount can be 800-900 rupees on actuals" (Personal interview on 22.2.2011). The non-affiliated member of the IEC of Private Hospital E also stated that trial subjects are given an allowance for follow-up visits but raised the difficulty faced by IEC members in deciding the criteria for payment to trial subjects and the IEC therefore "has to question" when an "allowance become undue inducement" (Personal interview on 6.4.2011).

- **Clinical trial registration**

With the WHO declaring that every clinical trial needs to be registered in a publicly accessible database, the DCGI made prospective registration of a clinical trial in India mandatory from June 2009 and entrusted the ethics committee with the task of ensuring registration as a condition to ethical review. Two IECs–of Public hospital A and Private Hospital D mentioned their role in ensuring clinical trial registration. An affiliated member from the IEC of Public Hospital A stated that only "temporary approval" is given to a clinical trial if it has not been registered in the Clinical Trial Registry of India (Personal interview on 25.11.2010). The manager of clinical research of Private Hospital D stated that clinical trial "registration is required even prior to enrolling the first patient" and the hospital ensures that provisional registration has been given to the particular trial (Personal interview on 23.11.2010)

- **Management of the IEC**

The Member Secretary of the IEC of Public Hospital A stated that while her role is "mainly secretarial work", everybody on the committee reads the protocols and "different members have different inputs" (Personal interview on 26.11.2010). The Member Secretary of Trust Hospital C also stated her managerial responsibilities of "setting the agenda for the [IEC] meeting, archiving" and correspondence with the investigators of trials (Personal interview on 22.2.2011).

- **Legal responsibilities**

The legal representative of the IEC of Private Hospital D stated that among other responsibilities such as checking the informed consent form he also examines the "medico-legal part" of a clinical trial for the protection of both the patient and the institution. The lawyer explained that "in any trial we have to see in case something happens to the patient...also check what claims the patient can file against the hospital and committee. I suggested that there should be an indemnity clause also for the ethics committee. So both the patients and ethics committee should be covered" (Personal interview on 20.12.2010).

b) None of the IECs make field visits to monitor on-going clinical trials. The IEC members are of the opinion that either the sponsor or a third party should be responsible for the role of monitoring trials.

All five IECs do not have any policy to visit trial sites of approved clinical trials. The only kind of on-going review undertaken by the committee is a desk review in the form of periodic progress reports, which, in the case of Trust Hospital C and Private Hospital D, are reports on serious adverse events, protocol amendments and other observations of the trial sent every six months to the IEC by the investigator. The Chief-Medical Excellence Programmes of Private Hospital D believes that the responsibility of monitoring a trial's progress "has to be with the investigator and the sponsor. If there is a problem the sponsor is informed immediately. If a patient in our site and in other sites in different parts of the world are having problems then the trial is either stopped or modified" (Personal interview on 10.11.2010). At an IEC meeting of Private Hospital D, attended by the researcher, the issue of monitoring was put on the agenda by the Chief of Medical Excellence Programmes. Responding to this, a senior non-affiliated doctor of the IEC suggested that the IEC should initiate surprise visits to the clinical trial site and appoint individuals to do the monitoring. (Attended

IEC meeting on 15.11.2010). However, this statement on monitoring by the non-affiliated member is no indication that the IEC will be conducting field visits. The Member Secretary of Trust Hospital C is of the opinion that "ethics committees cannot make on-site visits. Sponsored projects have CROs doing the monitoring" (Personal interview on 22.2.2011). The Member Secretary of the IEC of Public Hospital A claims that while "random checks" of trial sites "is very important", the IEC is not carrying out its role of monitoring approved trials—a job that should be done "ideally by a third party" (Personal interview on 4.11.2010). The Member Secretary of Public Hospital B was also of the opinion that a third party should be responsible for visiting the clinical trial site, unless a member on the IEC was specifically assigned the task of on-site monitoring of clinical trials. She stated that it was difficult for her IEC to make site visits due to shortage of manpower and an already overworked ethics committee.

c) There was limited deliberation on the complexities of the practical application of IEC responsibilities and limited understanding among IEC members of the scope of applying ethical principles in safeguarding the rights and interests of human trial subjects

While the majority of the IEC members, across different IECs were aware of the procedural requirements that their roles demanded, particularly with regard to matters of informed consent and insurance coverage for trial subjects, there was limited deliberation on the complexity of their roles. With the exception of the non-affiliated member of the IEC of Private Hospital E who questioned the problematic issue of undue inducements, no other members mentioned, difficulties in the practical application of some of their responsibilities such as: how do IECs ensure that trial subjects have understood the information on the consent forms that IECs closely examine or how is a favourable balance between risk and benefit assured or how do IECs ensure that the burden of research is not disproportionately borne by those groups with reduced autonomy or agency to protect themselves from making erroneous decisions with fatal consequences. While the Member Secretary of Public Hospital B implied that multinational companies prefer government hospitals because of large numbers of poor and unsuspecting patients, the member did not raise the issue of the equitable selection of trial subjects.

With the exception of the Member Secretary of Trust Hospital C who said that her IEC does not approve clinical trials of drugs that will not be accessible in India, the IEC members of other hospitals appear to take it for granted that clinical trials will take place in their respective institutions and approval will be eventually granted by the ethics committee without any deeper discourse on the fundamental ethical principles that should govern the conduct of clinical trials in the country. Without questioning the ethical principles of Beneficence, Justice and Respect for Persons in the initial stage of protocol review, the protection offered to trial subjects can therefore be confined only to the duration of the trial, and not applied to the processes before a trial takes place or after the trial is over.

The Chief of Medical Excellence Programmes, an affiliated member of the IEC of Private Hospital D was of the opinion that "the role of ethics is limited" (Personal interview on 10.11.2010). For another affiliated member from Private Hospital D "ethics is common sense" (Personal interview on 6.12.2010). While another affiliated member from Public Hospital A finds that the major ethical dilemma that she constantly has to confront (discussed in a later section of this chapter) is that "ethics committees are a big hurdle" to conducting "scientific experiments" (Personal interview on 1.12.2010). These statements made by doctors from different IECs indicate their perception that ethical considerations are a nuisance and a barrier to their work and that there is general resistance from medical professionals to engage in ethical discourse.

The response made by the legal representative on the IEC of Public Hospital A that ethics was not his specialisation and the doctors are the experts can be interpreted in several ways: firstly, as a lack of understanding on the part of the lawyer of his role on the committee and the potential of his legal acumen in the protection of the rights of the clinical trial subject; secondly, the lawyer's statement can be interpreted as a misconception about an ethics review as being the domain of medical professionals and thirdly, the notion of doctors as the experts on the IEC indicates the unequal context that underlies the relationship between the non-medical/non-scientific members on the committee and the clinicians or basic medical scientists (discussed further in another section of this chapter). The erroneous perception of the retired Hindi professor on the IEC of Public Hospital A, that he has only "a small" role to

play on the committee, which is confined to examining the language of consent forms, also indicates an inferiority complex on the part of lay members in IECs and the dangers of the multidisciplinary team dynamic where each member works in isolation with the other, perhaps, losing sight of the larger goal of human subject protection in clinical research.

The IEC of Public Hospital A has not thus far, organized any ethics training programme or orientation session for its IEC members (discussed in the section that follows). Lack of training in ethical principles and a lack of understanding in the nature and extent of an ethical review can leave IEC members unsure of the contribution they can make in evaluating the use of ethical principles in clinical research. The imperative of research ethics that uses human subjects needs to be underscored for non-affiliated members and also for medical experts who are not indoctrinated in ethics education. "Ethics is contrary to their [doctors] training... the human body is not of any consequence", claimed a non-affiliated and non-medical/non-scientific member of the IEC of Private Hospital E (Personal interview on 6.4.2011).

- **Differences and Similarities**

The non-affiliated members of the Public Hospital A appeared to be more limited in their understanding of the potential and scope of ethical review compared to the non-affiliated members of Private Hospitals D and E. Greater clarity in the responses of IEC members of private hospitals could be attributed to the training they have received on the role and functioning of ethics committees, where as Public Hospital A has made no provision for training its IEC members. The lack of training in fundamental ethical principles and their practical applicability could also be one of the reasons why ethics committee members are criticised for spending all their time on documents and procedures.

7. Training for IEC Members

Studies on ethics committees conducted in the U.S. and India have revealed that ethics committee members lack adequate professional competence that is required to perform their roles effectively. Majority of IEC members are not professional ethicists or individuals with some form of ethical experience (De Vries and Forsberg 2002; Brahme and Mehendale 2009). A study conducted in the U.S. specifically on non-

affiliated and non-scientist members found that almost half the participants expressed the need for education in science and ethics in order to strengthen their role as IEC members (Sengupta and Lo 2003). Members of the bioethics community believe that it is not enough to be "well-intentioned individuals" serving on an ethics committee (Hoffmann, Tarzian and O'Neil 2000:30). Training in ethics is essential for both clinicians and non-medical/non-scientific members especially in an atmosphere of growing complexity in the areas of clinical trial research such as genetics, the increasing number of large trials being run, the transition from single site trials to multi-centre trials as well as the increasing blurring of research and therapy, all of which have made the review of clinical research tedious and difficult (HHS, Office of Inspector General 1998). In addition, the vast financial investments in clinical research that demand a fast moving ethical review process has put pressure on IEC members to be both quick and efficient. While IECs can seek the advice of consultants—a facility also permitted for IECs in India—the provision to invite outside experts can be expensive and time consuming for ethics committees (HHS, Office of Inspector General 1998).

The ICMR guidelines—that only have a short paragraph on training for IEC members—state: "it is preferable to train the IEC members in Good Clinical Practice. Any change in the regulatory requirements should be brought to their attention and they should be aware of local, social and cultural norms, as this is the most important social control mechanism" (ICMR 2006:10).

Findings:

a) While the majority of IEC members emphasized the importance of ethics training, only members from Private Hospitals D and E have undergone some form of ethics training.

b) Two clinician/basic scientist members implied that ethics training was not necessary for medical professionals.

a) While the majority of IEC members emphasized the importance of ethics training, only members from Private Hospitals D and E have undergone some form of ethics training.

A manager from the department of clinical research at Private Hospital D, who functions as the secretariat for the IEC, believes that "training is important. We ensure

training, we invite experts. We explain the basics of drug development" (Personal interview on 23.11.2010).

Non-affiliated members from the two IECs—Private Hospitals D and E—that provide ethics training found the training experience to be useful:

> We did undergo training given by ICRI in Okhla. The training was useful. It was on the basics of clinical research, role of an ethics committee, responsibility of members of an ethics committee (Personal interview on 2.12.2010).
>
> I attended a workshop for members. It was very useful...I did not know until then that ethics committees have their origin in the Nazi doctor trials (Personal interview on 6.4.2011).

Although only members of the IECs of Private Hospitals D and E have undergone some form of training in ethics, more than half the members, including Member Secretaries of Public Hospitals A and B and the Trust Hospital C, acknowledged the importance of training in ethics and ethical guidelines. A non-affiliated member, who is a social scientist on the IEC of Public Hospital A, explained the difficulties faced by new IEC members due to the lack of training: "in the first two to three meetings we are like dumb people. But we are not showpieces" (Personal interview on 23.12.2010). The Member Secretary of the IEC of Public Hospital A said that "training is an issue" but has been unable to organize even a half-day training programme for the IEC because of the busy schedule of senior doctors who are also members of other committees. Taking time off from professional commitments to attend a training programme—that may not be a doctor's priority—in addition to being present at IEC meetings is a problem also faced by non-affiliated members: "If I wasn't retired I would not have set aside time for this [training]", said a non-affiliated member from the Private Hospital E (Personal interview on 6.4.2011).

b) Two clinician/basic scientist members implied that ethics training was not necessary for medical professionals.

An affiliated member, of the IEC of Public Hospital A, implied that training was not essential for doctors but mentioned the importance of developing discerning clinicians so that they can read between the lines of research protocols that are written by drug companies who are likely to prioritize their own business agendas:

> For clinicians, they are already sensitized, sensitive to patient issues, aware of ethical dilemmas so don't need intensive training like that but it would be good if somebody experienced in looking at protocols – these are technical documents provided by the pharmaceutical industry – could teach clinicians what to look for in these documents. The documents could be hiding information and not revealing everything. We also learn on the job (Personal interview on 25.11.2010)

Another affiliated member of the IEC of Private Hospital D also implied that ethics training was not such a necessity for doctors on the committee. "We are well aware of the role of ethics in clinical research", the member said. While admitting, "sometimes clinicians may not see things from a layman's perspective" and "there can be oversight which is not intentional", the member "takes ethics for granted". The affiliated member also stated the need for "capsules" to train non-medical/non-scientific members who cannot "just be there for the sake of attendance" (Personal interview on 6.12.2010).

While the two doctors from Public Hospital A and Private Hospital D did not see the necessity of ethics training for medical professionals, another affiliated member—the head of the department of anatomy—of the IEC of Public Hospital A felt that "there is need for ethics training not just for members of ethics committees but for all scientists. Ethics training is important when writing a project. Example, when we do a biopsy for cancer, we also take out a healthy lump. Is that ethical? No formal training is given right now" (Personal interview on 1.12.2010).

8. Barriers to the effective participation of non-affiliated and non-medical/non-scientist IEC Members

There is limited information on the experiences and perceptions of non-affiliated and non-medical/non-scientific members of IECs. From a few studies and reports we know that the non-affiliated and non-medical/non-scientific members are unable to contribute effectively to ethical review due to reasons of inadequate training, inter-group hierarchy in decision making and or over-emphasis on technical aspects of protocols which are not easily comprehended by this category of member (Sengupta and Lo 2003; Anderson 2006). A multidisciplinary group with the likelihood of having "no vested interest in the success or failure of the research" and who are more inclined to view the harms and benefits of a clinical trial from a trial subjects perspective is critical to the strength of trial subject protection systems (Anderson

2006:136). The contributions that non-affiliated and non-medical/non-scientific members can make to the welfare and protection of trial subjects and the understanding "that social science matters to bioethics" (Bosk 1999:49), is however, not given sufficient attention by institutions conducting trials and also by ethical policy makers.

More rigorous and formal training could expand the role of lay members beyond reviewing and scrutinizing consent forms and patient information. A report issued on IECs in the U.S. by the Department of Health and Human Services stated: "such [non-affiliated/non-scientific] members once sufficiently experienced and trained, can provide an important counterbalance to scientific and institutional interests. This may be especially important during the continuing review process when important questions" are raised, for example, with regard to the level of comprehension of trial subjects about the risks related to the research (HHS, Office of Inspector General 1998).

Studies conducted specifically on this category of IEC members have revealed that in ethics committee meetings the discussions tend to be dominated by affiliated members with scientific/medical backgrounds leaving little room for non-medical/non-scientific to express their opinions. In a study done on roles and experiences of such members, Sengupta and Lo found 88 percent of the participants had negative experiences with scientist members. These experiences included feeling disrespected by scientist members and not being taken seriously by them (Sengupta and Lo 2003). The report from the U.S. Department of Health and Human Services stated that while scientific knowledge is necessary for an ethical review it is not sufficient. The tendency to focus on technical or specialized inputs to an ethical review, the report states, can have a negative impact on ethical deliberations as investigators may choose to ignore issues such as risks involved in research and the equitable selection of subjects, and instead, focus on the scientific benefits of research. Non-medical/non-scientist members can thus counteract the tendency to neglect the actual purpose of an ethical review (HHS, Office of Inspector General 1998).

Findings:

a) Voices of non-medical/non-scientific members—across IECs—are not adequately represented during ethics committee deliberations.

b) In the responses of affiliated scientist members there is an underlying sense of condescension towards the non-affiliated and non-medical/non-scientist member.

c) Non-medical/non-scientific members across IECs are intimidated by the technically heavy protocols that pose a major barrier to their effective participation.

d) There is little awareness or reflection on the part of medical professionals in the contribution they can make to create a more conducive atmosphere to facilitate effective contributions by their non-medical/non-scientific colleagues.

e) The IECs lack a fundamental ethical framework and this absence of an overarching ethical structure translates into an IEC divided into two distinct camps: the medical expert and the non-medical/non-scientific members–that vitiates their overall goal of human subject protection.

Affiliated members from Public Hospital A and Private Hospital D, including the manager of clinical research from Private Hospital D, acknowledged the dominance of medical opinions during ethics committee meetings and the asymmetry in the group dynamic. They suggested training programmes to enhance and improve the contributions of non-affiliated and non-medical/non-scientific members to ethical review of research protocols.

> In most ethics committees doctors do the talking (Personal interview on 25.11.2010)
>
> They [non-affiliated, non-medical/non-scientific] usually keep quiet. Training will help and clearly define roles (Personal interview on 26.11.2010).
>
> I think if non-technical, non-medical members receive training they can participate and understand because for ethics committees participant protection is the main job and the PI [Patient Information] sheet and consent form is for them...forms are for the patient so you will understand as a non-medical member (Personal interview on 23.11.2010).
>
> Lay persons are ignorant about medical terminology or diseases. They should be explained in laymen's language (Personal interview on 7.12.2010).

With the exception of a non-affiliated/medical member, on the IEC of Private Hospital D, other medical members did not however express the need for sensitisation of doctors towards the problems of non-medical/non-scientific members and the

importance of achieving a balance in the scientific and ethical inputs provided during the review of a clinical trial protocol. The non-affiliated/medical member from Private Hospital D requested investigators during an IEC meeting to simply their protocols "so everyone can be involved" in the ethics committee meeting. During the one hour long IEC meeting of Private Hospital D where investigators presented their protocols there was not a single comment made or input given by a non-medical/non-scientific member (Attended IEC meeting on 15.11.2010).

In the responses of affiliated scientist members there is an underlying sense of condescension towards the non-medical/non-scientist member. The Member Secretary of the IEC of Public Hospital A stated that, "it is a good idea to organize a training for non-medical members" because it "will clearly define" their roles: "they can see if the Hindi translation is accurately done from the English translation. Is the patient information understandable to a layperson? Legal person is important in case RTIs [Right to Information] come up" (Personal interview on 26.11.2010). The Member Secretary of the IEC of Trust Hospital C with her statement: "the sociologist will go over each consent form", also suggested that the non-affiliated/non-scientist member's primary role is examining consent documents (Personal interview 22.2.2010). The Member Secretaries of both IECs, in their statements are essentially implying that non-scientist/non-medical members are only capable of examining the content of informed consent forms. The sense of disdain of the expert towards the role of the non-medical/non-scientist member is combined with a misplaced understanding of the responsibilities of non-medical/non-scientific members. The Member Secretary's statement on having a lawyer for RTI applications is not only an indication of a misinterpretation of the role of a legal representative on the committee but it also implies the Member Secretary's priority of protecting the institution from any liability. The first priority of a legal person on an IEC should be, however, to protect the rights of trial subjects and to apply legal expertise to interpret regulations and ethical guidelines for human subject protection and to ensure that sponsor or institutional interests do not conflict with those of the trial subject.

While doctors on IECs, like the Member Secretary from Public Hospital A, are no more experts of ethics and ethical guidelines than the non-medical/non-scientific members, the clinicians impose limitations on the role of this category of member—

who then conform to the limited expectation of their roles. For example, the lawyer on the IEC of Public Hospital A who the Member Secretary considers important for RTI applications, described ethics as "not my field. The doctors are the experts", (Personal interview on 16.12.2010).

An affiliated member on the IEC of Public Hospital A, rightly said that non-medical/non-scientific members "are appointed for a specific purpose" because "the crucial question is patient safety" and "ethics committees are looking for special inputs from non-technical members" (Personal interview on 25.11.2010), who are appointed to provide an ethical perspective and not only to ensure perfect consent forms. "But there are problems" says a social scientist on the IEC of Public Hospital A. The member explains why:

> We can't ask the doctors. Doctors are not conducive, they assert their knowledge of medical technology. They are afraid of the Chairman. He is hot tempered. It is a closed circle, they [the doctors] don't open up. At times I feel I am not doing justice. Three of us are from outside. We don't usually say anything. You have to be well studied if you say anything (Personal interview on 23.12.2010).

Other non-affiliated and non-medical/non-scientist members expressed problems similar to those of the social scientist member of Public Hospital A. A Hindi language specialist, also, on the IEC of Public Hospital A stated:

> We feel sorry to not have a medical background so that we can participate. The terminology is difficult. The most difficult challenge. I generally sit quietly because it is all medical (Personal interview on 30.11.2010).

Two non-members from the IEC of Private Hospital D stated:

> We have to sit through medical presentations for one hour. The investigators present what the sponsor has given. But we are interested in basic information (Personal interview on 2.12.2010).
>
> Protocols are sent to us before the meeting. These are huge documents and they send them because they have to by law but nobody has the time to go through them. People should be encouraged to send a summary by email. It is easier if a synopsis is sent to us (Personal interview on 9.12.2010).

A social scientist member from the IEC of Private Hospital E stated:

> Although there is a separate technical committee, for an ethics committee they [investigators] present the same information. It's a huge amount of literature

> and none of it makes sense. Nothing in the proposal says what the ethical issues are. There is no effort to make it easier (Personal interview on 6.4.2011).

The social scientist member from Private Hospital E also stated that ethics committee meetings are "intimidating" and "unless you have the confidence" to raise matters that concern the ethics of a protocol it can be difficult.

While, voices of non-medical/non-scientist members are not adequately represented in IEC meetings, the social scientist member from the IEC of Private Hospital E also stated, "that it is easier in a way for unaffiliated members to make a point" in an ethics committee meeting than for a clinician affiliated to the institution. Non-affiliated members, he explained, have less at stake in raising an objection than affiliated members whose disapproval could not only offend the Primary Investigator of a trial, who might be a colleague of the affiliated IEC member, but an objection from a doctor of the hospital could also displease the institution. Regarding the ability of non-medical/non-scientific members to raise objections in the presence of senior doctors, the social scientist member also stated that the composition of a committee is very important to the group dynamic. A supportive chair, the member claimed, that does not dismiss a non-medical/non-scientific member's observations can have a positive impact on the nature of interaction between the two types of members. The response of the social scientist from the IEC of Public Hospital A—who describes her Chairperson as a "hot tempered" individual and her IEC composed of "a closed circle" of doctors—appears to have a different experience from the social scientist of Private Hospital E.

Restricting the role of non-medical/non-scientist members and misinterpreting their mandate on an IEC leaves these members with little choice but to limit their role to examining consent documents: "if you are a lay person or legal person", says an affiliated member from Private Hospital D, "you will go straight to the patient information page because everything else is too technical" (Personal interview on 10.11.2010). A statement of a non-medical member from the same IEC, verifies the affiliated member's view: "They send us protocols a week before the meeting so we read the IC [informed consent] part to become aware of the IC forms" (Personal interview on 2.12.2010).

9. Death during a clinical trial

Schedule Y of India's Drugs and Cosmetics Rules and the ethical guidelines including the GCP guidelines explicitly state that the sponsor is responsible for reporting serious adverse events or adverse side effects of a drug/vaccine within two weeks of the event to the licensing authority. The investigator on the other hand has to report a serious and unexpected adverse event—that could be a death of a trial subject—to the relevant ethics committee within a period of twenty-four hours (Schedule Y, amended 2005, The Drugs and Cosmetics Rules 1945). While regulations on serious adverse events are clear, there are no guidelines for ethics committees on managing deaths that occur in trials and no policy mechanisms for holding sponsors/investigators/institution of trials accountable for trial subjects who have died during their trials.

It is rare for a pharmaceutical company to take responsibility for a death occurring during a trial, and investigations at the trial site or institution, if any, to ascertain the cause of death are most likely to be cover up operations that ascribe the cause of death to reasons other than the trial interventions. Two vaccine trials in India that received considerable media attention due to ethical violations clearly illustrate the ambiguity in the issue of accountability for a trial-related death and the circumventing of investigations into the actual cause of death. In the year 2008, an infant, who was wrongfully included in a clinical trial conducted at St. Johns National Academy of Health Sciences in Bangalore, died after being administered a pneumonia vaccine. The sponsor, Wyeth Ltd. denied the allegations and attempted to pass on the responsibility to the CRO who conducted the trial (Silverman 2008). In the course of the trials conducted to test the HPV vaccine in Andhra Pradesh, seven trial subjects—young girls between ten and fourteen years—died. Later investigations revealed that there were significant delays in reporting adverse events and deaths. Moreover there is no conclusive evidence on why the deaths occurred and report of the deaths of young girls were dismissed citing reasons such as malaria and snakebite (Press release on 9.5.2011).

Findings:

a) The transparency of investigations on trial-related deaths undertaken by Private Hospital E are questionable due to a clear conflict of interest of the investigation team.

b) There is no independent body—external to the hospital or trial site—responsible for investigating the cause of death that has occurred during a clinical trial.

The non-affiliated, social scientist member, on the IEC of Private Hospital E relates his experience of an ethics committee deliberation regarding the occurrence of a death during a trial that was being run by the institution. The social scientist member raised a question when a box in a form that required a 'yes' or 'no' answer for death related to a trial was marked 'no'. The IEC member raised the question about "the objectivity of the appraisal process by which it is decided that a death was unconnected with the research". The lay member's question about who decides if a death is related or not to a trial received a "stiff lipped" response from his colleagues on the IEC who stated that a special team—comprising doctors of the institution—had made the decision. The social scientist felt that his objection was perceived as "questioning the integrity of the specialist team". Since the IECs Chairperson did not engage with the issue during the meeting the member decided to "let it go for the moment" and did not "want to ask too many questions" (Personal interview on 6.4.2011). This particular experience of a non-affiliated member on an IEC indicates that regardless of the ability of an outside member to question the ethical practices of an institution, regardless of ethics training for members, voices of dissent can be dismissed by the majority and serious ethical concerns that arise in the course of a trial can be brushed under the carpet by the concerned institution.

10. Workload of IEC members

The sheer numbers of trials being run the world over (Angell 2004; Petryna 2009) has led to an increase in the workload of IEC members who essentially volunteer their time to attend ethics committee meetings. A report issued by the U.S. Department of Health and Human Services in the year 1998, discusses the increase in the workload of ethics committee in the U.S. This increasing work pressure on ethics committees, the report stated, is partly due to a rise in the number of adverse event reports and protocol amendments that the committee has to review but mainly due to a significant

increase in the number of protocols for initial review. As a result of the mounting work pressure the report states that IECs are struggling to cope with the increasing demands of the job. Several IECs lack support staff and cannot give adequate time to review each protocol. In addition, financial pressures faced by medical institutions are forcing several ethics committee members to devote their energies to financially lucrative clinical research (HHS, Office of Inspector General 1998). De Vries and Forsberg in their study on the functioning of IECs, used a survey to examine the workload faced by ethics committees. The questions in the survey included the number of IEC meetings, the length of the meetings and the number of "current active studies" of each IEC (De Vries and Forsberg 2002: 210). De Vries and Forsberg also state that almost "all criticisms of IRBs and all recommendations for change revolve around the need for support in the tasks of reviewing and monitoring research that uses human subjects" (De Vries and Forsberg 2002:210). Several institutions in the U.S. have adopted different strategies to cope with their increasing workload such as constituting more than one IECs and meeting once a week to manage the overload of protocols (HHS, Office of Inspector General 1998).

Based on a literature review of previous studies done on work pressures faced by ethics committees, the workload of IECs members in this study was assessed on the following criteria:

- The number of IECs in each institution. Some institutions have sub-committees that help in the distribution of workload of the IEC.
- The number of protocols or proposals reviewed in each meeting.
- The number IEC meetings in a month and the time and duration of each meeting.
- Separate committee for scientific review of protocols.
- The amount of time members have to examine protocols before the IEC meets.
- Secretarial support provided by the institution to the IEC.
- Field visits to clinical trial sites.

Findings:

a) There was a significant difference in the number of protocols reviewed per meeting of Public Hospital A, which had the largest numbers, compared to the number of protocols reviewed per meeting by the Private Hospitals D and E.

b) Although Public Hospital A and Trust Hospital C had the largest workloads, the IECs meet only once a month.

c) Greater institutional support was provided to members of IECs of Private Hospitals D and E and Trust Hospital C—compared to the Public Hospitals—to reduce their workload, in terms of dedicated administrative/secretarial staff and in appointing a separate committee for scientific review of clinical trial protocols.

Table IV.2 on the following page shows the differences in workload between IECs.

Table: IV. 2

Workload of Institutional Ethics Committees

Workload Criteria	Public Hospital A	Public Hospital B	Trust Hospital C	Private Hospital D	Private Hospital E
Nos. of IECs	3: 1IEC 1Sub Ethics Committee 1 Stem Cell Committee	1	1	3: 2 IECs (one is called IRB) 1 Stem Cell Committee	2: 1 IEC 1 Stem Cell committee
Scientific Review	Yes	Yes	No: Scientific Review is done by a Research Committee	No	No
Nos. of IEC meetings in a month	Once a month (the first Monday)	Once a month	Once a month (On second or third Wednesday)	Once a month	Every two months
Duration of each IEC meeting	3 ½ to 4 hours in the afternoon	2 ½ to 3 hours	The entire afternoon	1 to 1 ½ hours	2 hours
Nos. of trial protocols (new & old per IEC meeting	30 to 40 new protocols 5 to 10 old protocols	5 to 6 new protocols 5 to 6 old protocols	5 to 10 new protocols 30 old protocols	2 to 6 (old & new)	2 to 3 new protocols 10 to 15 old protocols
Time to read trial protocols prior to IEC meeting	10 to 12 days	7 days	15 days	Protocols are sent prior to meeting. Nos. of days not known	10 days
Periodic/update reports of on-going research sent by the PI	Every 6 months	Data not available	Every 6 months (Safety reports of drug trials monthly/once in 15 days	Every 6 months	Data not available
On-site visits	No	No	No	No	No
Administrative support dedicated to the IEC	No: IEC does not have a separate office or secretariat	Yes: A separate office and one part-time clerk	Yes: One full time scientist, one half time administrative person	Yes: A dedicated department of clinical research	Yes: IEC has a secretariat

From the table (IV.2) on IEC workload it is apparent that the IEC of Public Hospital A has the heaviest workload with its members responsible for the ethical and scientific review of about fifty protocols every meeting. Undertaking the scientific evaluation in addition to the ethical review of a protocol is a heavy burden on the IEC. An affiliated member stated that the IEC has "had a debate about the scientific review being separate. Some of us think it should be separate but there are clinicians in the group so it continues to be combined" (Personal interview on 25.11.2010). Although some of the IECs workload is shared by the Sub Ethics Committee who is responsible for reviewing student research projects, on the occasion when the Sub Ethics Committee is confronted with a difficult question or problem in its ethics review, the protocol is forwarded to the main IEC. The three to four hour long meetings of the IEC start at 2 pm, and "on a good day end at 5.30 pm and on a bad day at 6.30 pm", according to an affiliated member, are still not enough time to review the older protocols examined for amendments and serious adverse events (Personal interview on 25.11.2010). Although IEC members are given ten to twelve days to read the protocols, the "projects are many and so it is humanly difficult to do justice to all" expressed an affiliated member who is also the head of the department of anatomy. For another affiliated member, weekends are the only time he gets to read the protocols. If he gets two weekends before the IEC meeting it reduces the work pressure "but when we only get one Sunday then it's hard", the member said pointing to the large pile of protocols in his office, waiting to be read. As the numbers of protocols are large the IEC had also considered dividing the protocols among its members to lessen their workload but as of now the protocols are read by all members. The meeting schedule was also not convenient for all members, with a lawyer on the IEC wanting to resign because he was unable to attend meetings regularly on a Monday—a day he has to be in court. Unlike the IECs of the other hospitals, Public Hospital A has not provided its IEC with administrative support. The Member Secretary—the head of the department of Haematology—has to rely on the services of her personal assistant, assigned to the Haematology department, to keeping minutes of the meeting and other administrative tasks of the IEC. A major administrative challenge for the IEC "is filing and how well you can retrieve documents. These are important if an ethics committee has to function properly", stated the Member Secretary (Personal interview on 26.11.2010).

The IEC of Trust Hospital C follows the IEC of Public hospital A in its share of workload. "Every member puts in fifteen to twenty hours before the meeting", said the Member Secretary of the IEC of Trust Hospital C (Personal interview on 22.2.2011) The members of the IEC of Trust Hospital C review an average of thirty already-approved projects, new projects and those that have not yet been cleared by the committee.). Unlike the members of Public Hospital A, the work pressure for IEC members of Trust Hospital C is made easier by two staff members responsible for the management of the committee and the role of the scientific review assigned to a separate committee. The Trust Hospital C, however, does not have another sub committee to reduce the burden of work for its IEC members.

While the IEC of Public Hospital B is also responsible for the scientific review of research protocols like the IEC of Public Hospital A, its members have to review significantly fewer numbers of protocols per meeting. Unlike Public Hospital A, the IEC of Public Hospital B does have dedicated office space and one staff member. The support staff however, comprises only a clerical position. "That all I have", complained the Member Secretary who needs a "full fledged office and different levels of clerical staff to set the agenda, set dates for the meeting, look at the proposals". Currently, the Member Secretary is responsible for all these tasks "in addition" to her "hospital work which is so heavy" (Personal interview on 5.1.2011).

The IECs of the private hospitals of the study appear to have more institutional support than the public hospitals. While IECs of Hospital C, D and E all have secretarial support and separate scientific committees, the IEC of Private Hospital D has the most support from its institution of all five IECs studied. Private Hospital D has an entire department of clinical research dedicated to examining clinical trial protocols before the documents are forwarded to the IEC and is responsible for the regulatory and operational aspects of clinical trials conducted at the hospital. The team in-charge of regulatory affairs comprises a manager of clinical research, a coordinator of research and a statistician. Their responsibilities include:

- Signing of clinical trial agreements
- Ensuring investigators/sponsors are compliant with government guidelines
- Amendments made to protocols

The protocols are first examined and vetted by the manager of clinical research to ensure investigator compliance with required documents. If the paperwork is not complete and if all the requirements are not according to the Government of India's guidelines, the department with the help of a check-list, informs the investigator of the gaps in the documents such as patient safety information, adverse events information, and content of consent forms. The department of clinical research informs the ethics committee if the investigator does not comply with the changes suggested by them. Two ethics committees in Private Hospital D also share the task of ethical review and another committee does the scientific review.

While the IEC of Private Hospital E does have administrative support, according to the non-affiliated member, the "secretariat is mainly mechanical" and no effort is made to examine research protocols prior to IEC meetings in order to make it easier for members who are overwhelmed by the tedium of reviewing technical documents (Personal interview on 6.4.2011).

11. Ethical dilemmas and challenges that arise while reviewing a clinical trial protocol

An IEC may come across different ethical dilemmas while reviewing a research protocol. These ethical dilemmas can create a conflict of interest between an investigators and/or sponsors goal of achieving scientifically significant outcomes and an ethics committee's concern for ethical integrity in a clinical trial. Among the biggest dilemmas in the context of the global clinical trial today is the issue of access to care—a universal standard of care versus care that is locally available. The issue of what kind of care do people deserve especially in the developing world remains unresolved: should sponsors and investigators conduct trials in developing countries with the objective of testing interventions that are not the most effective and successful but the most affordable and sustainable for a developing country or should the best care be accessible to all subjects irrespective of economic concerns?

The randomized control trial poses major ethical problems. Those patients randomly assigned to the placebo arm of the trial will be denied treatment—especially problematic when placebos are used instead of known effective treatments exist. Investigators preference for the use of placebo even when known effective intervention exists is justified on the grounds that placebo controls allow for greater

scientific rigour and clarity in results (Resnik 1998). In attempting to balance scientific and ethical integrity in a project, "researchers may find themselves slipping across a line that prohibits treating human subjects as means to an end. When the line is crossed, there is very little left to protect patients from a callous disregard of their welfare for the sake of research goals" (Angell 1997: 847).

Findings:

a) The major ethical dilemmas and/or challenges raised by IEC members were use of controls in clinical trials, negotiating with sponsors regarding adverse event reporting and clinical trial agreements, inducements, selection of minor subjects and the originality of research protocols.

b) Members did not mention any other ethical challenges in conducting trials in developing countries such as access to beneficial treatment after the trial is over.

- **The use of controls in a clinical trial**

As mentioned in previous pages of this chapter, the hour long deliberations of the IEC meeting of Hospital D centred around the affiliated committee members questioning a trial's Primary Investigator—a doctor from the institution—about the use of a placebo arm when a known treatment exists for the particular condition under study. The investigator while recognizing the ethics committee's concern about the placebo reassured the members that the patients had only a ten percent chance of being enrolled into the placebo arm in that particular trial. "If there was no trial and the patient came to you then what would you offer him?" the IEC further questioned the investigator and requested the doctor to reassess the matter with the sponsor as patients of the hospital would be denied treatment. "The problem", one of the affiliated member's explained is that "for efficacy" investigators need to have a placebo arm in a clinical trial (Attended IEC meeting on 15.11.2010).

An affiliated member from Public Hospital A, who favoured the use of controls in a trial, expressed her most frequent ethical dilemma as an IEC member:

> Ethics committees are a big hurdle to conduct scientific experiments. We need more controls, we run short of numbers. Statistical evaluation is not up to the mark. This is the constant dilemma (Personal interview on 1.12.2010).

The need to balance the scientific and ethical integrity of a clinical trial protocol and make a judicious assessment of the research interests of the trial's sponsor, the compulsions of an investigator and the concerned institution, is a constant challenge that ethics committees must face if the overriding concern is to protect the trial subject–the most vulnerable party in the clinical trial.

- **Negotiating with multi-national pharmaceutical sponsors**

Among the main challenges while reviewing a clinical trial protocol for the IECs Member Secretary of Public Hospital B is negotiating with drug company sponsors regarding two issues: the disclosure of adverse reactions in the course of a trial and the Clinical Trial Agreement (CTA). According to the Member Secretary, drug companies are evasive about providing accurate information on adverse events. It is "the main issue" the member says, but "the sponsors try to make it seem not so serious" by claiming that adverse reactions can occur within seven days which in reality the member argues they could "go on for thirty days". Therefore, the Member Secretary states that the IEC tries to make sure that the "sponsor is liable" for adverse reactions (Personal interview on 5.1.2011). Another challenge for this IEC is to prevent MNCs from attempting "to get things done their way" and manipulating the Clinical Trial Agreement that the institution has drawn between the sponsor, Primary Investigator and the institution. These challenges, explains the member secretary, arise largely from dealing with "drug trial sponsors" and not "genuine research proposals such as postgraduate projects" that are funded by public institutions such as ICMR and the Department of Biotechnology (DBT), the Ministry of Science and Technology (Personal interview on 5.1.2011).

- **Undue inducement**

An ethical dilemma that was raised by the social scientist member from the IEC of Private Hospital E was about the issue of undue inducement. The member stated:

> Regarding patient follow up visits they are given an allowance. We have to question when does allowance become undue inducement? (Personal interview on 6.4.2011).

Inducements are usually monetary payments and or access to medical services offered to clinical trial subjects. The issue of undue inducement "is rarely explicitly and precisely defined" (Emanuel, Currie and Herman 2005:336) in both national and

international guidelines that essentially recommend that "payments should not be so large" (ICMR 2006: 25) so as to influence potential clinical trial subjects to make a decision about their participation which is against their better judgment. The decision, therefore, about a reasonable inducement is left to the discretion of the IEC.

- **Other challenges while reviewing a clinical trial protocol**

An affiliated IEC member from Public Hospital A, raised the point of investigators presenting a protocol of research that has already been done:

> We already know the answer to the question so why are you doing it all over again (Personal interview on 25.11.2011).

The member also expressed concern about the unnecessary use of age groups within the category of minor subjects:

> Studies that are using young children but don't have to include children, for example, between 5 to 12, but can include older age groups such as 12 to 18years, we suggest it to the investigator (Personal interview on 25.11.2011).

12. Administrative constraints faced by IEC members

In addition to workload, the professional challenges faced by non-medical/non-scientific members and ethical dilemmas that could arise in a protocol review, there are other constraints that IEC members face that pose obstacles to the smooth management of clinical research in their respective institutions.

Findings:

a) Difficulties in ensuring that sponsors provide documents that fully comply with regulations.

b) Pressure on the IEC to expedite the review process.

c) Ensuring regular attendance of IEC meetings.

d) Preventing Primary Investigators from leaving a trial before completion.

For those IEC members, such as member secretaries and managers, concerned with the administrative and operational aspects of an ethics committee—there are particular problems they encounter behind the scenes. For the manager of clinical research of the Private Hospital D—who is not an IEC member but has administrative responsibilities his "main challenge" is:

> Compliance [of sponsors]. Sponsors are always in a hurry. They think missing some things in a [Primary Investigator] PI sheet or consent form is okay but we have to check if everything is there (Personal interview on 23.11.2010).

For the Chief, Medical Excellence Programs of Hospital D:

> The biggest challenge is maintaining a quorum, getting attendance (Personal interview on 10.11.2010).

The Member Secretary of Public Hospital B related her experience with investigators demanding the IEC to expedite ethical review and not put unnecessary "hurdles" in the process of approval, especially in the case of a multi-site trial when ethics committees of the other sites have completed the approval process (Personal interview on 5.1.2010).

Two non-affiliated members from Private Hospital D, one with a non-medical/non-scientist background and one with a medical background, share the same concern of the high turn over of Primary Investigators on the same trial:

> In case the PI leaves in-between what will happen to the patient. The sponsor can say I will take my trial somewhere else. Ultimately the hospital is responsible for the subjects. So a co-PI should also be there so the patient is not deprived of treatment (Personal interview on 20.12.2010).

> Primary investigators should not keep changing because there is a break in the continuity and clinical data is important. It happens often because the industry is so dynamic that doctors keep moving jobs (Personal interview on 9.12.2010).

13. Remuneration for IEC members

Members of IECs, the world over, are not usually paid for their participation and serve on IECs on a voluntary basis (Williams 2005). However, some institutions provide honorary payments for attending ethics committee meetings. Guidelines have little or no mention on the subject of payment for IEC members. The ICMR guidelines state, that, "the members could be given a reasonable compensation for the time spared for reviewing proposals" (ICMR 2006: 20).

Findings:

a) Members across IECs were divided on the issue of payment.

b) Non-affiliated members in all IECs are given an honorarium or transport fee.

An affiliated member from the IEC of Public Hospital A was against the idea of payment for IEC members:

> Ethics committee members especially those in academic institutions, should not get paid. It's part of their job. We are not paid extra for examinations. On the other hand if you do pay then the chair or member secretary can question a member and ask why the person is not throwing enough weight on a particular protocol...the carrot has to be associated with the stick but more payment does not necessarily create accountability (Personal interview on 25.11.2010).

Another clinician from the same IEC of Public Hospital A was of the opinion that "outside members should be paid". She believes that all IEC members, in fact, should be paid, stating that other institutions provide "sitting charges" (Personal interview on 1.12.2010). A social scientist member also from the same IEC stated that members should get paid because, "It is a professional service. We spend energy, resources and time. For charity there are different places" (Personal interview on 1.12.2010).

A social scientist member from Private Hospital E was also of the opinion that IEC members should be paid, since payment could lead to greater commitment on the part of outside members, to attend IEC meetings. He believed that "getting an honorarium would not be the deciding factor to join an ethics committee but it does make a difference to motivate one to go to the meetings" (Personal interview on 6.4.2011).

While, the Member Secretary of Trust Hospital C, was of the opinion that ethics committee members should not be paid for their services, the Member Secretary of the IEC of Public Hospital B described her efforts to get the institution's permission for providing an honorarium for non-affiliated members of the IEC:

> We were giving nothing earlier. I also had to arrange for transport for all the outside members to come to the meeting. Now we give them something. I have been working on giving members an honorarium for two years now. I have finally got permission on paper. It was difficult because as an employee we are not supposed to get honorariums really and so I did not want to get involved with asking for money but outside members should get (Personal interview on 5.1.20).

The Member Secretary describes how the honorarium has made a difference to the attendance of IEC meetings and has also eased some of her administrative responsibilities:

> Since we started giving an honorarium everyone comes to the meeting. Earlier completing the quorum was very difficult. I had to keep chasing members. Now quorum is no longer an issue. I also do not have to arrange for transport anymore.

The Member Secretary also said "there is a flip side to paying. Some members come to the meeting without reading the proposals" (Personal interview on 5.1.2011).

- **Differences and Similarities**

Affiliated members of Public Hospitals A and B, of Trust Hospital C and Private Hospital E are not provided any payment for attending IEC meetings. Non-affiliated members of the IECs of Public Hospital A and Trust Hospital C are paid for only transport costs. Non-affiliated members of the IECs of Public Hospital B and Private Hospital D are given an honorarium. Non-affiliated members of the IEC of Private Hospital E receive an honorarium in addition to payment for transport.

14. Recommendations for India's ethical guidelines for biomedical research on human subjects

International guidelines for the protection of human subjects in biomedical research, such as the Helsinki Declaration of the WMA, and guidelines that focus particularly on research conducted in the developing world, such as those developed by CIOMS, have provoked controversies due to ambiguities on key issues—the most widely debated being the use of a placebo when an effective treatment exists. Other ambiguities in guidelines, as well as in FDA regulations (Williams 2005) are the result of limited direction given to IECs in managing complex ethical issues such as insurance for risk-related injuries, the risk-benefit relationship and undue inducements–discussed in greater detail in the previous chapter.

Indian ethical guidelines for biomedical research on human subjects, primarily, those of the ICMR and the Indian GCP that have been derived from international ethical guidelines and regulations contain some of the same ambiguities. For example, the Indian guidelines have also been critiqued for a lack of clarity on a sponsor's obligation to compensate trial subjects for trial related injuries (Thatte and Bavdekar 2009).

Findings:

a) Clarity on trial-subject insurance and payment for IEC members, restrictions on physician-investigators and registration for IEC were the recommendations given by the members.

b) The IEC members did not mention the necessity for ethical guidelines to provide clearer instruction on complex ethical issues such as definition of minimal risk and post-trial access.

c) Not all members had read the ethical guidelines.

Both non-affiliated and affiliated members across IECs had recommendations for additions to be made to the Indian guidelines for biomedical research on human subjects.

- **Rules for investigators**

Two members, an affiliated and non-affiliated from Private Hospital E expressed concern about the excessive number of clinical trials being run under one Primary Investigator of the hospital and questioned the commitment of physician-investigators to the protection of trial subjects.

The non-affiliated member stated:

> Too many trials are going on. Are doctors really interested in the trials or is it pecuniary advantage? Who is gaining from these trials...is it the doctor who gets free trips to present findings or is it the patient...I have seen how doctors are pulled out of surgery to come for a meeting. They work on such tight schedules where do they have the time for trials (Personal interview on 9.12.2010).

The affiliated member stated:

> The investigator's role is important...he should be vigilant. Number of clinical trials by one individual should not be too many so he can supervise the trials in a proper manner. Three to four trials is too much because then patients won't be taken care of properly (Personal interview on 7.12.2010).

These members recommended greater stringency in investigator oversight:

> There should be a dedicated investigator team for clinical trials (Personal interview on 9.12 .2010)

> There should be more elaboration on the PI's responsibilities. If you look at the U.S FDA rules the investigator has a lot of responsibilities...There should be a limit on the number of clinical trials an investigator can do (Personal interview on 7.12.2010)

Questioning the integrity of the physician-investigator due to his or her involvement in multiple trials simultaneously appears to be a concern specifically for Private Hospital D as the Chief of Medical Excellence Programmes also commented on the need to investigate if "the doctor is doing too many trials" (Personal interview on 10.11.2010).

- **Clinical trial registration**

An affiliated member from Private Hospital E recommended the need for a guideline for the registration of all ethics committees in the country.

- **Insurance**

The manager of clinical research from Private Hospital D expressed the need for greater clarity in the guidelines on the issue of an insurance policy for clinical trial subjects:

> In the Indian GCP some parts are vague. For example in the international guidelines details are given about insurance but in the Indian guidelines there are no details so sometimes we are not sure what to do. So we need more details (Personal interview on 23.11.2010).

> Guidelines should be clear on insurance for subjects. They should have a rough template of a [Clinical Trial Agreement] CTA so all institutions can follow that. Right now our legal expert has made a CTA (Personal interview on 5.1.2011).

The Member Secretary of Public Hospital B who invested considerable time and energy in providing non-affiliated members on her IEC with an honorarium also recommended the need for greater clarity in the guidelines on the subject of payment for IEC members.

- **Reasons why some members did not have recommendations**

A social scientist member from the IEC of Public Hospital A stated that she had not been given any ethical guidelines at the time of joining the IEC and therefore could not make any recommendations.

> We are not given any guidelines to read. In fact...I should read the guidelines to know my role. Next time I should ask about guidelines (Personal interview on 23.11.2010).

Another non-affiliated member of Public Hospital A was also unsure in his response on the issue of ethical guidelines being provided by the hospital. The responses on guideline recommendations of the two (of three) non-affiliated members of Public Hospital A stood in contrast to the more informed responses of three non-affiliated members of Private Hospital D. It can perhaps be suggested that the differences in the responses of non-affiliated members of two different IECs, is due to the training programme that was provided to IEC members of Hospital D whereas no training was given to members of Public Hospital A.

The Member Secretary of the IEC of Trust Hospital C stated that the ICMR guidelines are clear and it is the ethics committees that are not aware of their roles.

> We cannot introduce changes in the Guidelines. The ICMR guidelines are clear. The rules are clear. The problems with ethics committees are that they don't know (Personal Interview on 22.2.2011).

An affiliated member from Private Hospital D, on the other hand, was dismissive of the use of ethical guidelines: "guidelines should be there", the member said, "but ethics is common sense" (Personal interview on 6.12.2010).

15. Relevance of research

Only ten percent of research on drugs is focused on conditions that comprise ninety percent of the global disease burden (Petryna 2009: 194). It is not clinical trials per se that are the problem but the concern that multinational drug trial sponsors are conducting trials in the developing world to primarily study those diseases or health problems that are the concern of developed nations. The key question raised therefore is: are clinical trials being conducted in countries like India relevant to the public health needs? Adriana Petryna and Arthur Kleinman argue that, "decisions about what therapeutic entity to develop are connected to institutional priorities that may have little to do with the realities of disease and treatment demand (Petryna and Kleinman 2006:7). An analysis of industry sponsored clinical trials registered on the U.S. clinical trial registry from the years 2005 to 2007 shows that cancer is the disease being focused on by the industry (Karlberg 2008). An analysis done by Clinical Trials Watch of trials that were registered on India's clinical trial registry found that foreign sponsors, including drug companies, who are the main sponsors of trials in India, did not prioritise diseases that contributed significantly to India's disease burden. In the

month of June, 2010, only 16 of the total 1078 registered trials (1.48 percent) were on lower respiratory infections and only seven of 1078 (0.6 percent) were on TB, with foreign sponsors spending their resources primarily on cancer—with 13.4 percent of trials dedicated to cancer research (Ravindran and Ingle 2010).

Findings:

a) Sponsors of trials do not prioritize diseases or conditions that occupy a large share of India's disease burden.

Members who responded to the issue of the relevance of clinical research being done in India corroborated the findings of Clinical Trials Watch. They acknowledged that international sponsors of clinical trials in India do not give sufficient attention to research on diseases that occupy a large share of India's disease burden.

The Member Secretary of Public Hospital B remarked:

> They [MNCs] are making India a dumping ground. Studying drugs of all types that we don't use (Personal interview on 5.1.2011).

An affiliated member of Public Hospital A stated:

> I agree that they [pharmaceutical companies] are not looking at neglected diseases (Personal interview on 25.11.2010).

The members also justified the multinational pharmaceutical industry's clinical research priorities. They argued that foreign sponsors should not be responsible for public health in India when the state had failed to deliver health care based on the needs of the people.

An affiliated member from Private Hospital D explained:

> We've had malaria and TB since we were children there are so many other diseases now.

An affiliated member from Public Hospital A:

> But why should a pharma company do malaria drug trials? They are commercial, looking for profit. It's the government's responsibility, world over governments are giving up their role of social responsibility so why should a pharma company care.

A non-affiliated member with a medical background stated:

> Research on malaria, dengue is zero because they [developed countries] don't have patients. Pharmaceutical companies are not doing charity they are looking for drugs that can generate revenue. Not many new molecules are being developed [in India] (Personal interview on 7.12.2010).

"Of course then one can say that physicians should not do trials of diseases that are not relevant", said the affiliated member from Public Hospital A who defended the physician who is willing to participate in a study that may not necessarily be beneficial to India:

> For a doctor's career, for promotional aspects it is important to be published in an international journal like *Science*, [*New England Journal of Medicine*] NEJM. These won't be publishing on Malaria unless it is a path breaking study but 80-90 percent of studies are not (Personal interview on 25.11.2010).

A social scientist member on the IEC of Private Hospital E—where only cardiac related trials are conducted—stated that his time on an ethics committee had him insight into the enormous pressure that the industry imposes on physician-investigators.

> It's apparent that this is corporate driven research. Ethical issues are commercial considerations. I am used to the academic world. In the social sciences proposals are passed on the merits of the case. Here you have corporations. I sensed the pressure that researchers are under (Personal interview on 6.4.2011).

16. Projects and sponsorship

The fact sheet of Clinical Trials Watch categorises the different kinds of sponsors of clinical trials in India into two broad groups of Indian and non-Indian and further categorised these into public, private, non-profit, institution or agency and pharmaceutical company. The fact sheet reveals that the largest number of sponsors of clinical trials in the country are foreign sponsors, followed by Indian and collaborative clinical research projects respectively. Of the foreign sponsored projects, the foreign drug companies occupy the biggest share (Ravindran and Nikarge 2010).

Findings:

a) Research projects can be developed by physician-investigators who belong to the institution or research can be generated by agencies/institutions not associated with the hospital.

b) The largest sponsor of clinical trials in Public Hospital B, Trust Hospital C and Private Hospitals D and E is the multinational pharmaceutical industry.

- **Sponsors**

Clinical trials reviewed by the IECs of this study are sponsored either by Indian drug companies, multinational pharmaceutical companies or other private/international agencies as well as Indian government agencies such as ICMR and DBT.

According to an affiliated member of Public Hospital A, "trials are both pharmaceutical industry sponsored and investigator-generated trials" with the latter, "typically funded by a government agency" (Personal interview on 25.11.2010). In Public Hospital B and Private Hospital D, multinational pharmaceutical companies and "transnational corporations" (Personal interview on 6.4.2011) are the main sponsors of clinical trials. In Trust Hospital C, the Member Secretary claimed that sixty percent of the trials conducted by the institution are sponsored by the pharmaceutical industry, the rest being supported by government agencies such as DBT. According to the Chief of Medical Excellence Programmes from Private Hospital D, "most of the trials are sponsored by MNCs" because "India has not generated a single molecule" (Personal interview on 10.11.2010).

- **Projects**

The clinical trials are either investigator led studies which are trials generated by doctors from within the institution, or trials that are generated by private sponsors who then approach the selected institution to conduct the trial. Public Hospital B does not permit investigators from outside the institutions to conduct trials and even those trials "sponsored by MNCs [Multinational Companies] are conducted by our own doctors", stated the IEC Member Secretary (Personal interview on 5.1.2011). In Private Hospital D, the trials can be "investigator led studies" conducted by doctors from within the institution and in the case of multinational sponsored trials where the hospital "is selected as one of the research sites" the doctors from private hospital D can also be selected as a co-investigator and not a PI—unlike in Public Hospital B.

Clinical trials at Private Hospital E are conducted by doctors who work at the hospital.

In Public Hospital A, the sponsor typically approaches a former faculty member of the hospital—associated with the particular condition under study—to initiate the communication process with the institution. As far as Private Hospital D is concerned, the CRO is permitted direct access to its doctors. The sponsor or CRO can directly approach a doctor of the institution requesting the doctor's participation in a clinical trial. If the potential investigator of the trial is in agreement, the CRO or sponsor will conduct a feasibility study of the institution following which permission to conduct the trial will be requested from the DCGI.

17. Reasons for ethical violations in clinical trials in India

Although India has constituted ethical guidelines for biomedical research on human subjects and is attempting to tighten its regulatory framework there have been several accounts of ethical violations in clinical trials being conducted in the country that have exposed clinical trial subjects to great risk and sometimes with fatal consequences. Moreover there are also accounts of ethics committees and the DCGI—key regulatory bodies for human subject protection—failing to perform their roles of ethical review effectively and responsibly (see chapter two for unethical clinical trials).

Findings:

a) All members acknowledged that prevention of ethical violations is the primary responsibility of the IEC and any lapses are due to ethical oversight of ethics committees.

Two affiliated members—from Public Hospital A and Trust Hospital C—incriminated ethics committees for ethical violations in the conduct of clinical trials in India.

An affiliated member from Public Hospital A, was appointed to assist an enquiry committee that investigated ethical violations of clinical trials conducted to test the vaccine for HPV—the cause of cervical cancer—on young girls from impoverished tribal communities in the states of Andhra Pradesh and Gujarat (see chapter two).

Regarding the role of the ethics committee in the HPV trials, the affiliated member stated:

> I think the ethics committee is partly to blame. You can't pass a protocol without giving it full ethical clearance. Informed consent was taken in a hotchpotch manner. In India things are not done methodically. In a primary centre an ANM will take consent for the patient...the parents should have been informed properly. Wardens [of a Hostel] can't take consent (Personal interview on 1.12.2010).

The examination of informed consent documents—the responsibility that ethics committee members, particularly external members, claim to focus on—was neglected in the HPV trials. The inability of the ethics committee in ensuring compliance with the requirements for consent forms before a clinical trial begins questions the commitment of ethics committees to perform the most fundamental and basic duties of an IEC.

The Member Secretary of Trust Hospital C was also of the opinion that ethical violations are taking place due to inefficient ethics committees:

> Because ethics committees are not doing their job properly. Most ethics committees are not spending time on protocols. Projects are looked at today and given approval tomorrow (Personal interview on 22.2.2011).

Affiliated Members from the IEC of Private Hospital D, that conducts clinical trials sponsored largely by multinational companies, expressed the need for IECs to be vigilant of the commercial agendas of the international pharmaceutical industry.

> Data is money. Why are foreign pharmaceutical companies coming to India, Africa and China? Because resources are cheap, manpower is cheap. So ethics committees have to make sure that people are not being exploited (Personal interview on 6.12.2010).
>
> No doubt there is the unseen hand of the pharma but they can't do anything they feel like unless you sell your self. We have not allowed many trials even though it has meant that [the hospital] is losing money (Personal interview on 6.12.2010).

Another member—non-affiliated—from the IEC of Private Hospital D expressed the need for the IEC to closely monitor the investigator:

> Violations take place because the investigator is not being vigilant. For example using a drug approved for cancer cannot be used for something else.

Random checks should be done by ethics committee members to check for quality (Personal interview on 7.12.2010).

18. Investigator presentation at ethics committee meetings and processing fees

The IECs of Trust Hospital C and the two Private Hospitals D and E require the Primary Investigator or a co-investigator of a clinical trial to present new projects or protocols at ethics committee meetings (see Table: IV.3). The non-affiliated member of the IEC of Private Hospital D stated that there is a backlog in the number of protocols to be reviewed due to the absence of PIs at ethics committee meetings. For the IEC of Public Hospital A that reviews between 40 to 50 protocols per meeting, investigator presentations are considered time consuming.

Some IECs require sponsors/investigators to pay a processing fee (see Table: IV.3). The IECs of this study charge a one-time processing fee as opposed to instalments paid in the course of a trial. While Public Hospital A does not charge a fee, Public Hospital B charges a fee of rupees 10,000. According to the Member Secretary of the IEC of Public Hospital B, although the fee is utilised toward payment for the honorarium of IEC members, the system of charging a processing has been ad hoc, based on "whoever can pay. But now we have decided to charge drug companies a fee" (Personal interview on 5.1.2010). For Trust Hospital C, the processing fee for ethical review applies to projects sponsored by pharmaceutical companies and other private sponsors. The money is used toward the salaries of the IECs administrative staff and for the general functioning of the ethics committee.

Table: IV.3

Investigator Requirements	**Public Hospital A**	**Public Hospital B**	**Trust Hospital C**	**Private Hospital D**	**Private Hospital E**
Investigator Fee (in rupees)	No	10,000	25,000	50,000	Data not available
Investigator Presentations at IEC meetings	No	Data not available	Yes	Yes	Yes

19. Summary of essential findings

- There is no transparency or instituted policy for appointing IEC members.
- Only the Private Hospitals provided ethics training for IEC members.
- There is no on-site monitoring of clinical trials conducted by IEC members.
- The Private Hospitals and the Trust Hospital C had greater resources to support their IECs and assist them in managing the workload compared to the Public Hospitals.
- There is no guideline or regulation to manage deaths in the course of a trial.
- Non-medical/non-scientist members expressed difficulty in comprehending highly technical research protocols.
- Findings allude to an unequal interaction between affiliated members and non-affiliated/non-medical IEC members.
- Non-affiliated/non-medical members are not able to fulfil their purpose on an IEC.
- Members of IECs can lose sight of their primary goal of human subject protection due to pressures exerted by the institution and demands from sponsors/investigators to expedite the process of ethical review.
- The majority of IEC members did not question the underlying structural inequality of the kinds of trials taking place in India today or question their relevance to the public health needs of the country.
- While IEC members may have good intentions, they do not have the time to thoroughly examine clinical trial protocols, especially in the case of Private Hospital A and Trust Hospital C that review 30 to 40 protocols per meeting held every month.

Conclusion

Although the study cannot be used to make generalisations for IECs in the city of Delhi or the country, certain key considerations emerge from the findings.

The constraints and challenges faced by IEC members from selected hospitals in Delhi are similar to challenges faced by IEC members in the developed world. For example: inadequate administrative support for IECs, limited or no ethics training for IEC members, the assessment of informed consent being confined to only documentary evidence, the absence of a member recruitment policy, increasing workload of IECs due to large numbers of protocols for review, barriers faced by non-medical/non-scientist members in making effective contributions to ethical review,

irregular attendance of ethics committee meetings and the lack of IEC accountability in the public domain—that are among the findings of this study, are also issues central to the critique of IEC functioning in the U.S. and the reasons for an appeal to reform the regulatory structure.

The similarity in the nature of problems that plague IECs in India with those of the developed world can be attributed to the mere replication of an already flawed regulatory mechanism for the protection of research subjects in biomedical research. The Indian state has adopted guidelines on the role and functioning of ethics committees from the West without acknowledging the many aspects of an IECs role that have not worked in developed countries. Ethics committees in India are expected to adhere to rules and regulations that have been conceptualised without adequate understanding of the gaps between ethical guidelines and the realities of conducting clinical research, particularly in a developing country like India that has a highly privatized health system which is unaffordable to the majority of its people. There is not enough reflection on "the unequal contexts in which research is being performed and about how conditions of inequality are at present facilitating a global proliferation of pharmaceutical drug trials" (Petryna 2005:183).

The inroads made by the global drug industry in directing clinical research agendas for investigators and medical institutions—that are largely profit driven rather than based on equity and public health needs of host countries—is evident from the responses of the IEC members. The industry-driven and industry-dependent clinical trial with its enormous commercial potential has provided incentive to hospitals to invest in the running and management of clinical trials. The findings of the study indicate that the IECs of private hospitals are more professionally and efficiently run than the public hospitals. The private medical institutions have greater resources available to build capacity of its ethics committee members and its physician-investigators and to create a clinical trial infrastructure of a high standard so that it can meet the needs of the clinical trial industry. These needs have to do with ensuring compliance with clinical research regulations and expediting protocol review and paper work leaving no time for IEC members to think about the larger ethical issues of the trial under review.

There is, therefore, an urgent need for each individual IEC member to recognize the immense scope of an ethics committee's role in the clinical trial process and the enormity of moral responsibility towards the research subject. While an IEC cannot prevent the state sanctioned growth of a clinical trial industry or change the structural inequality of a clinical trial process, it does has the legislative authority to disapprove any clinical trial protocol if it fails to comply with the ethical principles of Respect for Persons, Justice and Beneficence. Apart from the DCGI, the ethics committee, is the only other agency sanctioned by law who can attempt to mitigate the unequal conditions under which industry sponsored clinical trials are being conducted in the country today.

Chapter Five

Concluding Discussion

No matter how advanced clinical knowledge becomes, the human research subject will always be central to the progress of medicine. Historically, medical experimentation has take advantage of human desperation and targeted the most disadvantaged and impoverished sections of society for its research. What has changed is not the desperation of the research subject or the risks and uncertainties inherent in clinical research but the very structure and scope of the clinical trial. The clinical trial enterprise today is built on the foundation of a business model fostered by its major player, the multinational pharmaceutical industry, together with biotechnology firms and public funded research conducted in American academia. It transcends national boundaries because the primary objective for the key actors is the search for profitable investment opportunities. A clinical trial can involve multiple trial sites using thousands of research subjects across the world. With the widening of the scope of a clinical trial has emerged an entire industry devoted to efficient clinical trial site management and producing good quality data, which if produced in a site like India, should be acceptable to regulatory standards in the West. Alongside the industry, a complex regulatory structure has also grown because once the state has sanctioned the growth of a clinical trial industry it must at the same time also regulate it. Disclosure about heinous medical experimentation on humans conducted in the West during the War years and after, and those in the developing world that continue to this day, led to the development of an extensive ethical and regulatory structure for the protection of the human subject in biomedical research. The clinical trial regulations and ethical guidelines of the West have been replicated in India to a certain degree. Central to the regulatory framework, as far as human research subject protection is concerned, is the ethics committee. The welfare of the research subject is no longer dependent on a physician-investigator's good conscience. Now, the ethics committee is the key oversight mechanism to ensure that the investigator and the clinical trial sponsor do not neglect their moral duty of ensuring the safety of the trial subject over and above the scientific goals of research. An ethics committee in the course of ethical review of research must actualize the three ethical principles of Respect for Persons, Justice and Beneficence.

The ethics committee in India was however disadvantaged from the start, more so than its Western counterparts. Institutional Ethics Committees in India operate in a time when clinical research has become more complex and competitive and the rules for conducting a clinical trial are also more elaborate than before. They have to contend with the complicated issues that arise because the majority of the drugs being produced are not significant improvements over existing ones, intellectual property regimes are undermining drug manufacture in the developing world and diseases that cause significant morbidity and mortality in the developing world are not prioritized enough by the global drug industry. In addition, trial subjects from the developed world are no longer available to provide the large numbers necessary for a drug to pass the marketability test, so there is enormous pressure to test ever increasing numbers of human subjects in developing countries.

The IEC today has to ensure the protection of a growing number of vulnerable subjects being drawn into clinical trials sponsored largely by the drug industry whose chief concern is to expedite the approval process. Its members are not adequately trained and neither are they sufficiently motivated to provide the much-needed layer of protection between the research team and the trial subject.

Representatives of regulatory affairs departments of CROs—the middlemen in a clinical trial operation—perceive the ethics committee as a body that can be easily manipulated and appeased by tinkering with the contents of a clinical trial protocol. Investigators are often doctors working in the same institution where the trial is conducted and are likely to be colleagues of ethics committee members. Ethics committee members, overburdened with large numbers of protocols to review as well as administrative responsibilities, have neither the time nor the resources to visit clinical trial sites. They therefore function in complete isolation of clinical trial subjects whose welfare and rights is their primary responsibility before, during and after a clinical trial is over. Moreover, ethical guidelines that are meant to point ethics committee in the right direction are continuously evolving documents providing limited clarity on ethical questions that have no easy answers. Current legislation for clinical trials is not stringent enough and the legislative powers of an ethics committee are limited. Ambiguities in guidelines and weak legislation makes the work harder for ethics committee members who have to rely on their discretion, moral judgement and

ethical expertise to make the right decisions, while simultaneously balancing relationships with the scientific community.

The institutional ethics committee in India is functioning in the context of crises. Members of ethics committees work within a systemic crisis and also in a crisis of public health and poverty (Petryna 2009). The systemic crisis that the IEC inherited from the West needs urgent fixing. All IEC members need to be trained and oriented to their role, and the nature of the training and definition of ethical expertise also needs clarity. Clinicians need to be sensitized to the roles of non-medical members and the institution needs to commit greater resources to ensure the smooth running of an ethics committee. The composition of an IEC and the criteria for selecting members needs more consideration. Should all IEC members be selected from outside the institution? Should the IEC be a public funded body? These are the kinds of questions that need to be discussed and debated. The inability of ethics committees to visit clinical trial sites in order to prevent ethical violations from taking place is another serious concern. Should clinical trials be monitored by a third party as some IEC members of this study suggested? Or would another regulatory agency only add to the bureaucracy of the clinical trial process and further distance the trial subjects from the people who are supposed to ensure their protection and safety? These are questions that need to be urgently addressed by the country's regulatory authorities and all those concerned with the ethics of the clinical trial. A greater body of knowledge is needed on the functioning of ethics committees that are currently being run without transparency and accountability across the country. While the Indian government has recently introduced draft legislation for regulating CROs, the mandatory registration and regular appraisal of ethics committees is also essential.

Critics like Kaushik Sunder Rajan argue that the practice of ethics in clinical trials in India is limited only to regulatory procedures. India's crisis of public health and poverty, the larger context in which ethics committees function, is neglected in the review of a trial protocol that exposes socially and economically disadvantaged people to risks that may provide no direct benefit to them. Ethics committees, for example, do not spend time investigating the process used to select people for clinical trials or question access to treatment after the trial is over. The regulatory and ethical framework, contrary to its objective, facilitates the pharmaceutical company in

recruiting large numbers of trial subjects at low costs. Once the content of the consent documents has been examined, other paper work completed, and the consent form signed, the ethical review required to start a clinical trial is complete.

The pharmaceutical industry conducts clinical trials not because of its concern for the health of people but because trial subjects generate "value" for the industry. Sunder Rajan uses the Marxian analysis of surplus value to explain the concept of "surplus health" produced by clinical trials (Sunder Rajan 2007:67-88). The machine at the time of industrial capital was used to enhance the potential of labour that was greater in value than the wage of the labourer; similarly, research subjects in a clinical trial are used by pharmaceutical companies to produce "surplus health" (Sunder Rajan 2007: 67-88). This generation of surplus health is made possible by the drug industry that tests drugs that have the potential to be consumed later by those who can afford to be part of the drug market. The clinical trial needs research subjects to be exposed to invasive procedures and risks to develop drugs for customers in a neo-liberal society for whom "surplus health" is created, just as industrial labourers were exposed to risks while operating machines. Research subjects in India are therefore risking themselves for drugs that will not necessarily benefit them or their community.

In a crisis of poverty and public health, the role of an ethics committee becomes limited to some extent. Ethical guidelines and regulations, no matter how stringent and streamlined, cannot change the structural inequalities that underlie the global clinical trial. This argument while essential and central to the role of ethics in clinical trials in India, offers no solution to prevent ethical violations in clinical trials. The media is increasingly reporting clinical trials that have exposed trial subjects to unnecessary harm, disability and even death. That unethical conduct in clinical trials becomes public knowledge only after the violation has occurred is a clear indication of the failure of the current ethical and regulatory structure to ensure the safety of trial subjects. While strengthening ethical review and monitoring will not bring structural change and alter the inequality of the global clinical trial, it can prevent ethical violations from occurring. Since the trial subject's only option for protection is the ethics committee, it is imperative and urgent that the cracks in the system are repaired. The reform must however bring robust change to the ethical review of clinical trials that brings the IEC closer to the realities of clinical research in India.

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