CLINICAL TRIALS ON HEALTHY VOLUNTEERS: EXPANDING THE FRAMEWORK OF EXPROPRIATION

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CERTIFICATE

This is to certify that this dissertation entitled **"CLINICAL TRIALS ON HEALTH VOLUNTEERS: EXPANDING THE FRAMEWORK OF EXPROPRIATION"** is submitted in partial fulfilment of six credits for the award of the Degree of MASTER OF PHILOSOPHY of Jawaharlal Nehru University. This dissertation has not been previously submitted for the award of any other degree of this university or any other university and is my own work.

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

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Contents

List of Abbreviations

ARAGR	Average Relative Annual Growth Rate
B.Pharm	Bachelor of Pharmacy
BGPMUS	Bhopal Gas Peedith Mahila Udyog Sanghatan
BGPSSS	Bhopal Gas Peedith Sangharsh Sahayog Samiti
BMHRC	Bhopal Memorial Hospital and Research Centre
BMHT	Bhopal Memorial Hospital Trust
CDER	Centre for Drug Evaluation and Research
CDSCO	Central Drug Standard Control Organization
COPD	Chronic Obstructive Pulmonary Disease
CRO	Contract Research Organization
DCGI	Drug Controller General of India
DNA	Data Not Available
DNA	Deoxyribonucelic Acid
EC	Ethics Committee
ECG	Electrocardiogram
EOW	Economic Offences Wing
EU	European Union
FDAAA	Food and Drug Administration Amendments Act
FICCI	Federation of Indian Chambers of Commerce and Industry
GCT	Global Clinical Trials
GDP	Gross Domestic Product
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
ICMJE	International Committee of Medical Journal Editors

ICMR	Indian Council of Medical Research
IEC	Independent Ethics Committee
IMR	Infant Mortality Rate
IND	Investigational New Drug
IVF	In Vitro Fertilization
JAACAP	Journal of the American Academy of Child and Adolescent Psychiatry
LG	Lallubhai Gordhanbhai
MAA	Marketing Authorization Application
MCI	Medical Council of India
MCO	Managed Care Organizations
MGM	Mahatma Gandhi Memorial
MIC	Methyl-Iso-Cyanate
MLA	Member of Legislative Assembly
MMR	Maternal Mortality Rate
MoHFW	Ministry of Health and Family Welfare
MYH	Maharaja Yeshwantroa Hospital
NCE	New Chemical Entity
NDA	New Drug Application
Net En	Norethisterone Enathane
NIH	National Institutes of Health
NIHR	National Institute of Health Research
NRHM	National Rural Health Mission
OHRP	Office for Human Research Protections
PI	Principle Investigator
PIL	Public Interest Litigation
RTI	Right to Information

SAE	Severe Adverse Event
TRIPS	Trade Related Intellectual Property Rights
UK	United Kingdom
US	United States
USFDA	United States Food and Drug Administration
USPHS	United States Public Health Service
VVF	Vesico Vaginal Fistulas
WHO	World Health Organization

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Introduction

On 10th October 2011, Dr. Surinder Singh, Drug Controller General of India (DCGI) during a presentation in front of pharmaceuticals and Contract Research Organization (CRO) representatives in a meeting at the Institute of Clinical Research (India), Mumbai said that India will be a preferred destination for clinical trials (Singh 2008). He cited a number of reasons like medical infrastructure, trained and English speaking human resource and large, diverse and treatment naive patient pool which can fulfil the demands of outsourcing trial molecules. He also assured that the office of DCGI will establish a single window and fast track clearance for approvals of clinical trial proposals, especially of global pharmaceutical trials, along with tax holidays for trial related investments. At the end of the presentation he said that, 'We Indian believes in: "Let us not follow a path set by others. Let us set a path for others to follow' (Singh 2008: 32). But the truth is that India was actually walking on a path set by the era of *neoliberal revolution* and so called revolution in life sciences technology (Cooper 2008).

As Foucault put it, the development of the modern life sciences and classical political economy should be understood as parallel and mutually constitutive events. According to him, the classical period of science divided the nature into mineral, vegetables and animals. In the early nineteenth century, there was a fundamental shift from the classical science of wealth (mercantilists and physiocrats) to modern science of political economy. The classical period used to see value as a function of the trade, circulation and exchange while the modern political economy attributed it to time-processes of labour force. In parallel to it, there was a shift from natural history of the classical period to the modern biology and modern life sciences. It was perceived that there is a fundamental difference between the organic and inorganic and it gave a way to the articulation of notion of labour as a fundamental originary source to all value (Cooper 2008). As the work of Ricardo cites,

> .....value for the first time ceased to be a mere sign of equivalence, circulating in the flat world of representation, and came to measure and measured by something other than itself: the expenditure of force in time, "the human being who spends, wears out and waste his life" (Adam Smith and David Ricardo)

So in this period the production was the ultimate source of value and human being as a valuable creative force of the production. The second departure to the understanding of life was during the mid twentieth century when welfare or the social state came as a first political form and brought administration of demographics for the economic growth. It took the responsibility of the productive life of the labour as well as reproductive life of the nation for the economic growth of the nation. State was analyzing the composition of the population and intervening in the process of reproduction to make the population economically productive force. It took the responsibility of the life of its citizens but reciprocally it imposed obligation on its citizen to give their life to the nation.

Further around 1970s, it was realized that Fordist manufacturing economy has its own limits and has entered into a regime of irreversible decline. To deal with this crisis, in the era of neoliberalism, there was a fundamental shift from industrial economy to innovation based economy. The biotechnology and pharmaceutical industry shared a major part of this innovation based economy with a common ambition to overcome the ecological and economic limits to growth associated with the era of industrial production, through a speculative reinvention of the future. In this phase, the commercial processes entered in to the life sphere of the people at a micro level. During this phase the life at cellular level was put at work and human bodies were used for the experimentation. In United States (US), as a result of this, US President Ronald Reagan implemented series of reforms to mobilize the revolution in the field of research in life sciences, health and biomedicine which promised to deliver new technological solutions to human problems (Cooper 2008). Revolution in biotechnology and advances in genetic engineering resulted in a number of compounds that were coming out of laboratories, waiting to be tested for its therapeutic value. As the former United States Food and Drug Administration (USFDA) Commissioner Mark McClellan said while addressing a meeting of researchers in 2003, 'There are more investigational new drugs, more experimental treatments today...than ever before' (McLellan cited in Shah 2006: 3). But the pace at which new drugs were coming out was far more than the capacity to carry out clinical trials and obtain USFDA approval. As a result, there were tremendous delays before new drugs could enter markets. The reasons were obvious: the process of experimentation of investigational drugs and producing reliable data is intensely

time and resource consuming. Also, the rules and regulations in traditional hubs of clinical research became strict as several clinical trials related tragedies got exposed. The clinical industries in the developed countries were using the Black and marginalized population of their country as guinea pigs for the experimentation. Ultimately US government had to step in to put the regulations in place to protect the rights of the Black population. *Belmont Report (1979)* and *National Institute of Human Research Act, 1993* were the regulations by government to regulate the clinical trials in the US (Fisher and Kalbaugh 2011). On the other hand, several Asian countries were rising as a hub of clinical research. These countries such as India, Russia and China, tried to create a positive environment for the clinical research by deregulations of clinical trial industry and offering other benefits such as tax holidays (Srinivasan and Nikarge 2009). This resulted in an exodus of global clinical trials to these countries. The Average Relative Annual Growth Rate (ARGAR) of these countries was tremendously high as compare to traditional regions where the actual growth rate was negative.

In India, following the amendment in Schedule Y of the Drug and Cosmetics Act in the year 2005, the *phase lag* was removed which allowed conduct of trials of New Chemical Entities (NCEs) (MoHFW[1] 2005). This also allowed phase I trials and concurrent phase II and III trials in India. As per past experience in the process of drug development from the laboratory to final drug, out of 100 NCEs just about one reaches the final goal of becoming a drug for human use. Most of these NCEs never actually become medicines (Branch and Agranat 2014). In fact many of the NCEs failed the test of USFDA approval at the time of scrutiny of the NCE application itself. According to study done by Sacks et al., of 302 NCE applications reveals that 151 applications were rejected by the USFDA at first place (Sacks et al. 2014). The main reasons for rejection were inadequate drug performance and incomplete study proposals. Out of the rejected application 71 applications were accepted after resubmission even though safety deficiency of these drugs was similar to never approved drugs. Another study by Lurie et al. did an analysis of letters of non approval of marketing application issued by USFDA revealed that around 49 per cent of letters cited the deficiencies in the safety and efficacy domains (Lurie et al. 2015). That means, except the trial of successful medicine which reach till market

[1] Ministry of Health and Family Welfare

approval, majority of remaining NCEs trials must have produced the some kind of Severe Adverse Events (SAEs) in the participants. Within a subset of clinical trials of NCEs, the phase I trials are non-therapeutic and participants of these trials are called *healthy volunteers*. They are designed to test the toxicity of the substance; response of human body and extent to which drug is absorbed and excreted from the body. Ultimately, they are designed to determine critical dose amount above which it will produce adverse effects on the human body. Hence the phase I trials are always likely to produce some adverse effects in the participants (Fisher 2015). Therefore it resulted in a series of clinical trial tragedies in India. Following a petition in Supreme Court of India in the year 2012, it was revealed that around 17,778 participants suffered with SAEs out of which 3458 were deaths during clinical trials (Swasthya Adhikar Manch 2012). It also came to light that poor people living in the slums and villages, children and women were the main target of these clinical trials. There were serious violations related conduct of trials like proper consent process was not followed; on one hand doctors received huge financial incentives while victims did not get any compensation and many more.

Unlike the participants of phase II and phase III who participate in a trial with a hope of better and free medical care, the phase I trial participants participate in the trials with a financial motive (Fisher and Kalbaugh 2012). The current discourse of the discussion regarding healthy volunteers is mainly focussed on archetypal conception of ethics which assumes that individual is motivated by some altruism to contribute in the scientific research for the larger good of the humanity. This conception considers that good research is a one in which proper informed consent is taken and guidelines for Good Clinical Practices (GCP) are followed. But it selectively ignores the influence of larger social, cultural, economic and political realities which influence the individual's decisions (Fisher 2013). There is a fundamental question, why do people participate in the trials in spite of knowing that the risk and probability of the SAEs is high. Several researchers argue that apart from socio economic background, repetitive participation leads to banalization of risk (Fisher 2015). But questions remain about the motivation behind the first time participation. The limitation of all these studies is that it analyzes the risk in the clinical trial setup and fails to go beyond. It does not take into consideration the daily threat, violence and uncertainty of life posed in the daily experiences outside the clinical trial setup.

It also fails to incorporate the historical shared experiences of violence and threat of the trial participants which results in underestimating the risk in the trial setup.

Hence this study try to explore the historical and present expropriation experiences of the clinical trial participants, especially healthy volunteers of phase I trials. Historical vulnerability can be traced through the Marxian analogy where availability for the capital was generated by pre-existing violence that has created a property less proletariat (Marx 2013). The vulnerability in a present form can be analyzed through its analogy with labour-capital industry setup where wage is used as materialized contractual form through which individuals' are freed from serfdom and converted into the workers for capital (Sunder Rajan 2007). These workers are then forced to work at starvation wages and their surplus labour was exploited to generate the profit for the capital industry. The failure of the Fordist economy transformed the economy into innovation based economy where life at microlevel was exploited. This transition in human life and the experiences of the exploitation has been shared within family and in the larger society. It influences the decision making of the people to participate in the trials, the risk they analyze and their own understanding of the commodification of their bodies.

The qualitative and exploratory research design was used to study the phenomenon of expropriation. The researcher has tried to explore the daily life experiences, historical expropriation of the family members which contribute in the normalization of risk in phase I clinical trials. Clinical research especially phase I trials in India are conducted clandestinely in a very secretive manner. On the one hand, healthy volunteers are not willing to disclose that they do participate in the trial and earn money through that. On the other hand in the name of conducting ethical research and maintaining confidentiality of clinical trial participants the CROs usually are not ready to disclose the names of participants. Therefore it is hard to find healthy volunteers who are participating in these trials. Hence the method of snowball sampling was adopted by the researcher to find these cases. The researcher acquired the contacts of all the referred cases through a participant from Mumbai and an agent from Ahmedabad. A total of ten cases were interviewed comprehensively with the help of the interview guidelines prepared. As mentioned above, although the snowball and purposive sampling was used, the researcher has also tried to select the cases so that sample could be diversely represented based on variables such as

women, SAEs cases, schedule castes and schedule tribes, minorities and agents in clinical trial industry. The researcher has accordingly conducted a thorough interview of the healthy volunteers, three from Mumbai and five from Ahmedabad. The Researcher has also interviewed two agents who are husband wife duo who had initially worked as healthy volunteers.

Chapter One describes the trends of globalization of clinical trials. It also elaborates upon different push factors which were responsible for the outsourcing of the clinical trials to emerging destinations like China, Russia and India. To match with the intent of global pharmaceuticals of outsourcing clinical trials, the emerging nations prepared the grounds to attract the global clinical research industry and its investments. There are a number of pull and push factors cited by different studies. This chapter attempts to analyze the validity of the each factor based on available facts. It also specifically tries to analyze the trends of clinical trials in Indi and factors which were responsible for the growth of clinical trial industry.

Chapter Two describes the clinical trial tragedies specifically in the US and in India. Substantial numbers of trials are still conducted in the US and it is still an epicentre of the trial industry. But recently the US have shown negative growth in the clinical trials. Numerous incidences like the historical Tuskegee syphilis study tragedy, experiments of Dr. J. Marion Sims symbolizes racism in medicine, misconduct in human research and government abuse of Black people (Brandt 1978; Gamble 1993; Ojanuga 1993). These incidences have predisposed many African American to distrust human research lead to low Black people participation in the human research (Gamble 1997). Further, in this chapter, it has been described that, though participation of the Black population is low in a clinical research as a whole, the phase I participation of the Black and other minorities is very high. The vulnerability and marginalization forces them to participate in the phase I trials for monetary benefits. Following the same, the several clinical trial tragedies across India which has caused number of deaths and other SAEs across have also been elaborated.

Chapter Three is an analysis of the data collected from the interviews of the healthy volunteers. The initial part elaborates on the methodology of the study following which each case has been briefly introduced. A numbers of themes have been come out of the qualitative analysis of the data. Caste based discrimination, impact of

globalization, gender based violence, displacement of slum dwellers were some of the expropriation experiences of the people. It is a clearly coming out of the study that throughout the life span, healthy volunteers and their families have faced life of violence, threats and challenges. All these factors have culminated in shared experiences of poor and disenfranchised people results in the banalization of the risk in a clinical trial.

Chapter 1

Globalization of Clinical Trials

1.1 Introduction

Clinical trial is a fundamental part of the drug development process worldwide. It is the only method to certify the efficacy and safety of a new drug molecule for human use. In recent decades, there has been a tremendous growth of clinical trials in the countries of the developing world. There are two ways of looking at these trials. One view raises serious societal concerns and consequences over the growth of clinical trials along with issues of ethics, informed consent and patient rights. The second view looks upon the growth of clinical trial industry as an economic opportunity which will nurture the development of the clinical and drug discovery research in the country and ultimately will contribute to the economic growth of the country. This kind of conceptualization which focuses on either *All black* or *All white* sides of the terrain of clinical research will fail to address the larger complex issues related to clinical research (Bajpai 2013). As clinical research is very much at the centre in drug development process, the approach should be to 'get things right' by addressing issues of ethics, regulation of clinical research, patients' and participants' rights in terms of informed consent and issues related to human rights (Bajpai 2013). In the Indian context, there is a need to make sure that the research is methodologically and culturally valid and human rights of participants of the trials must be guarded. Before entering into these issues, let us first glance through some of the basics of clinical trials.

1.2 Phases of Drug Development Process

Drug development has three major phases (Tonkens 2005):

A) Pre-clinical Research and Development

During this phase, the invented molecule is tested on animals to determine its toxicity, carcinogenicity and kinetics. If the molecule is found effective then an

Investigational New Drug (IND) application is made to the concerned authority seeking permission to test it on human beings.

B) Clinical Research and Development

Whenever a new drug is discovered by drug companies for use of human beings, it is necessary to conduct clinical trials in order to study the safety and efficacy of the new drug on the human beings. The term 'Clinical Trial' has been defined under *Drugs and Cosmetics (2nd Amendment) Rules, 2005*. This definition under Rule 122DAA of the Rules reads as follows:

> For the purpose of this Part, "Clinical Trial" means a systematic study of new drug(s) in human subject(s) to generate date for discovering and/or verifying the clinical pharmacological (including pharmacodynamic and pharmacokinetic) and/or adverse effects with the objective of determining safety and/or efficacy of the new drug (MoHFW 2005: 1)

There are mainly two objectives of clinical trials of a particular new molecule or treatment device or treatment regimen discovered. Firstly, the clinical research attempts to determine whether the particular molecule discovered is safe for human consumption or not and if yes, what is the quantity/dose of that molecule safe for human consumption. Later phases check the efficacy of that drug for particular disease along with other physical properties. Hence this is the only exclusive method to determine the efficacy and the safety of the drug. Certain scientific standards are prescribed all over the world in order to protect participant's rights and safety along with production of reliable data. This is again divided into four phases.

***Phase I*:** This is also called as *first in human* trials. In this phase, a small number of healthy volunteers are involved to check the safety of the compound, the safe dose for the compound, any severe or other adverse reactions, pharmacokinetics and pharmacodynamics. The inpatient period of healthy volunteers is from one or two days up to a week with follow up the may last for about a month. Many compounds do not pass the test of phase I.

***Phase II*:** During this phase, the trial molecule is given to the patients of disease for which the drug is intended and it involves a few hundred patients. Special care has to be taken to select the patients with *pure* disease form with no inter-current diseases.

There are two sub phases of phase II clinical trials. Initial phase II trials are called phase IIa trials which are basically pilot trials to determine the safe dose range. As it carries a greater risk, they tend to be conducted at medical universities under specialized investigators. During second sub-phase of the trial, phase IIb, efficacy of the compound in treating the disease for which it is intended is determined. Other aspects like safety, pharmacodynamics and pharmacokinetics are also examined because sometimes the response of healthy volunteers and patients are different.

Phase III: This phase involves thousands of patients to determine the different routes of administration, different doses of the standard drug against the standard regimen or to test a new drug against the standard treatment. This phase contains a number of pivotal studies which are mandated to demonstrate safety and efficacy in a large number of patients. The participant's sample may include selected population with all forms of the disease or conditions to be treated and may be on multiple medications. If the drug has been approved with less than two pivotal studies, it requires post marketing commitments to validate its results in phase IV. The research design for these trials is randomized, usually placebo controlled and it often involves an active comparator. These are mass trials with thousands of patients participating all over the world and might often comprise investigators with less expertise. The cost of these trials is high and some estimates claims it costs US$50 to 100 million per trial. After successful completion of this trial, the New Drug Application (NDA) is made to the concerned authorities seeking permission to market the drug.

C) Post-marketing Phase

Phase IV trial is usually called as post marketing trial. The objective of this trial is to gather more data on long term risks or benefits of the drug or data on side effects and safety. Some people view that, rather than serving any scientific purpose, phase IV trials are simply an excuse for the companies to finance the doctors to put more patients on already approved drugs (Bajpai 2013).

Unlike the phase II and III trials, which are therapeutic trials, phase I trials are non-therapeutic and designed to test the toxicity of the substance, response of human body and up to what extent drug is absorbed and excreted from the body. Ultimately, they are designed to determine critical dose amount above which it will produce adverse effects on the human body. Hence the phase I trials are always likely to

produce some adverse effects in the participants (Fisher 2015). Apart from this, in the case of phase I trial, the volunteers who do participate, are the healthy. Unlike the other phases of clinical trials where you may get therapeutic benefits, phase I trial participants gets only monetary benefits. Hence it is very important to look into issues of healthy volunteers in order to protect the rights of these participants.

1.3 Scenario of Indian Clinical Trial Industry

Clinical trials being carried out in India can be broadly classified in two categories, namely, Pre-approval Clinical Trials with the purpose of allowing import or manufacture for use by people; and Clinical trials of New Chemical Entities (NCEs), also called new drug substances or investigation new drugs. If the ethical processes of conduct of trials are followed, pre-approval trials are considered as helpful to trial participants and also introduce new medicines in the country. But there are many complex issues around the conduct of clinical trials of NCEs. The approval to conduct of clinical trials on NCEs was first introduced in India by amendment made in the rules in January 2005. NCE is referred to as Investigational New Drug in Rule 122DA of the Drug and Cosmetic Rules 1945 (MoHFW 2005). NCEs are entities which are mostly discovered and patented by pharmaceutical companies in the developed countries and have to undergo all stages of trials, from animal trials to phase I, II and III human trials, before they can become new drugs. The law was amended in January 2005 in favour of drug development industry by allowing phase I trials, concurrent phase II and III trials in India. As per past experience in the process of drug development from the laboratory to final drug, out of 100 NCEs just about one reaches the final goal of becoming a drug for human use. Most of these NCEs never actually become medicines (Branch and Agranat 2014). The purpose of conducting NCE trials on humans is ultimately to obtain marketing approvals in the country of origin of the NCEs. The patients in the developed countries are now extremely aware of the potential risks of the NCEs. Apart from that, regulations related to the conduct of clinical trials are very stringent in these countries which delay the process of approval of trials. Conducting human trials in these countries is difficult and very expensive for the multinational pharmaceutical companies (Bailey et al. 2008). On the other hand, in the developing countries which are emerging as a

future destination for drug development industry, the trial subjects are either poor healthy volunteers or patients of the doctors who trust them with their lives, consume whatever medicines their doctor prescribes without questioning. The laws in these countries are inadequate; implemented in a negligent manner and conducting human trials is easy and cheap (Srinivasan and Nikarge 2009). The reason why these trials are being conducted is to obtain market approval and to fulfil the criteria of specified minimum number of subjects. The conduct of these trials in India cause minimum benefits to the people of this country. Rather it allows foreign companies to use Indians as guinea pigs in these trials (Nundy and Gulathi 2005). Once these NCEs are approved as medicines by the Drug Authorities of the countries of their origin, they are marketed all over the world including countries where no trial takes place.

Ever since the gates to the NCE trials were opened to allow human trials of untested NCEs in India, more than 1500 NCEs have been tested between 2005 to 2012 in India (Swasthya Adhikar Manch 2012). As per the Parliamentary Committee Report, the office of Drug Controller General of India (DCGI) seriously lacks in capacity to technically evaluate the applications seeking approvals of these types of trials. The Parliamentary Committee have cited documentary evidence to prove that the some opinion of experts is nothing but dictates by drug companies (Parliamentary Standing Committee 2012).

The regulatory framework in India is not in the interests of trial subjects (Srnivasan and Nikarge 2009; Swasthya Adhikar Manch 2012). Once the trial is permitted by the DCGI, the entire responsibility of monitoring of trials has been given to the Ethics Committees (EC). The law permitted trials to be conducted by individual doctor in their private clinics and private hospitals after getting approvals from EC. Strangely, a new category of ECs has been introduced in the year 2005. They are called Independent Ethics Committees (IEC) which are not part of any institution. As per law as it stands today any seven to twelve private individuals can constitute themselves as IEC (MoHFW 2005: 31). However these ethics reviews were very inadequate. They were not established as per legal provisions; members were lacking capacity for detail, and institutional support was not given to them to conduct thorough reviews. An Indian Council of Medical Research (ICMR) survey found that only 40 of 179 IECs follow the prescribed legal provisions and function as per

various ethical guidelines (Mudur 2005). They were not accountable to anybody and have been giving approvals on commercial considerations.

Most of the trials that are being conducted in India are on *Care-cum-trial* basis[2]. It means that patient who approaches doctor for treatment are enrolled as subjects for clinical trials. These patients are vulnerable because of the relationship and respect for doctors for treatment forced them to get enrolled as subjects for clinical trials. Therefore they routinely accept enrolment in such trials. Many times patients do not even know that they have become subjects of trial due to illiteracy, poverty and ignorance. If such patients who are converted to subjects of clinical trials suffer any serious injury or die as a result of trial, the investigator who has an obvious conflict of interest determines whether or not injury or death occurred due to the clinical trial. As a result, even though between years 2005 to 2013, 3458 people have died and 14,320 have suffered through SAEs, only 89 deaths and 506 SAEs have attributed to clinical trials. Out of 3458 deaths, compensation was offered to only 89 deaths which were attributed to clinical trials. Regarding 506 SAEs, the Ministry of Health and Family Welfare (MoHFW) said that, there was no law to compensate SAEs other than deaths. So compensation has not been paid in these cases. MoHFW does not have information about deaths and SAEs after year 2013 (Swasthya Adhikar Manch 2012).

1.4 Trends in Globalization of Clinical Trials

1.4.1 Global Trends of Clinical Trials

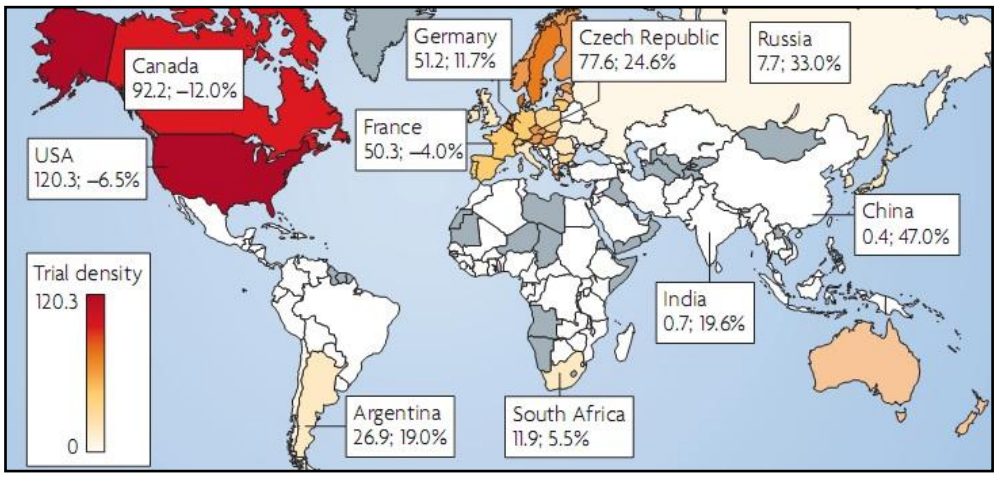
Traditionally the wealthy and developed countries, especially countries from North America and Western Europe have been the epicentre of the clinical research. But in recent years, a shift of pharmaceutical industry sponsored clinical research to the emerging regions such as Eastern Europe, Latin America and Asian Countries has been observed (Thiers et al. 2008). In these regions, specifically India, China, and Russia have noticed tremendous growth in clinical research (Ladin 2008). Though currently a majority of clinical trials are conducted in developed countries, the rate of

[2]Data analyzed till 2008 shows that almost 85 per cent of the trials are phase II and phase III trials (Nikarge and Pamnani 2009).

increase of clinical trials in traditional regions is decreasing tremendously while it is increasing in emerging economy countries.

Figure 1.1

Density of Actively Recruiting Clinical Sites of Biopharmaceutical Clinical Trials Worldwide



Source: *Trends in the globalization of clinical trials* (Thiers et al. 2008: 14)

Note: Density is in per country inhabitant (in millions; based on 2005 population censuses); darker orange/red denotes a higher density. The trial density and average relative annual growth rate in per cent is shown for selected countries. The countries in grey had no actively recruiting biopharmaceutical clinical trial sites as of 12 April 2007 (Thiers et al. 2008).

One study conducted by Thiers et al. in the year 2007 suggests that though traditional countries are still dominating in hosting number of trial sites, they are showing negative growth. The US have dominated it by a very large margin, having more than eight times (36,281 trial sites) the number of trial sites than second ranked Germany (4214 trial sites). The top five countries i.e. US, Germany, France, Canada and Spain were all from traditional regions and together they were hosting around 66 per cent of the global trials. But the trend to be noticed here is about countries from emerging regions. Though these countries are small players and individually were hosting on an average two per cent of the trial sites, as a group they were hosting around 17 per cent of the trials. However, emerging nations have grown rapidly from an almost negligible in just several years. It can be seen through their high Average Relative Annual Growth Rates (ARAGR) (See Figure1.1) which is positive for all

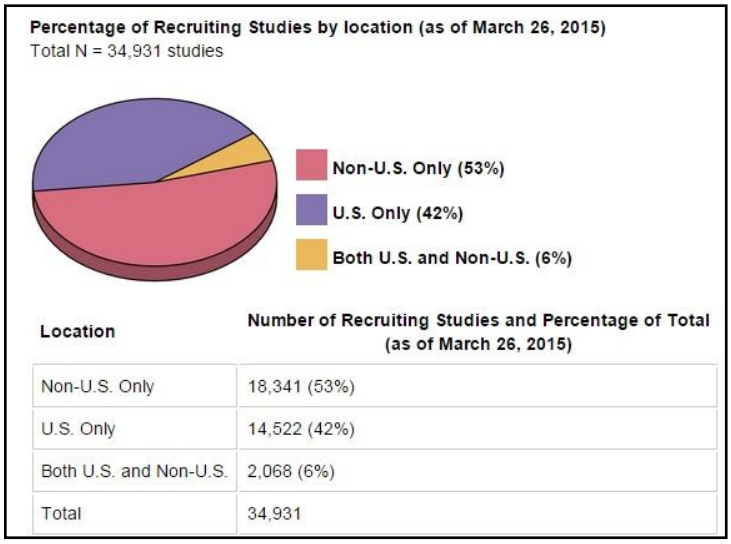
emerging countries while on the other side almost all tradition countries are showing negative growth. In terms of growth rates ranking, 24 of the fastest growing 25 countries are from emerging regions while 19 of the 25 slowest growing top 50 countries are from traditional regions (Thiers et al. 2008).

A study conducted by U.S. Department of Health and Human Services[3] found that the number of foreign principle investigators who are seeking United States Food and Drug Administration (USFDA) approval has increased sixteen fold between 1990 and 1999 (Shah 2006). Apart from this, it has been also observed that multinational pharmaceutical industry were seeking approval of over sixteen hundred trials overseas from USFDA by year 2004. A.T. Kearney Report[4] states that roughly half of the 1200 US clinical trials in 2005 used international sites (Shah 2006). In 2007, over 60 per cent of the studies submitted to Centre for Drug Evaluation and Research[5] (CDER) contained data from one or more sites, apart from the US (Shah 2012). The latest data from USFDA shows that 53 per cent of locations are non-US that are recruiting participants for the study while US has only 42 per cent of recruiting sites (Ayalew 2013). While principle investigators dropped in US by 11 per cent, the number of investigators in non-US sites increased by eight per cent between 2001 and 2003. The post 2005 period has seen a major boost to multicentre, multinational trials outside the US. The pie chart below depicts latest percentage of recruiting studies by location. (See Figure 1.2).

[3] It is a cabinet level department of the US federal government with a motto of improving health, safety and wellbeing of American people.
[4] A.T. Kearney report is published by A.T. Kearney global management consulting firm describing global trends of different industrial sectors.
[5] Centre for Drug Evaluation and Research is a part of U.S. Food and Drug Administration (USFDA) which regulates over-the-counter and prescription drugs, biological therapeutics and generic drugs

Figure 1.2

Percentage of Recruiting Studies by Location

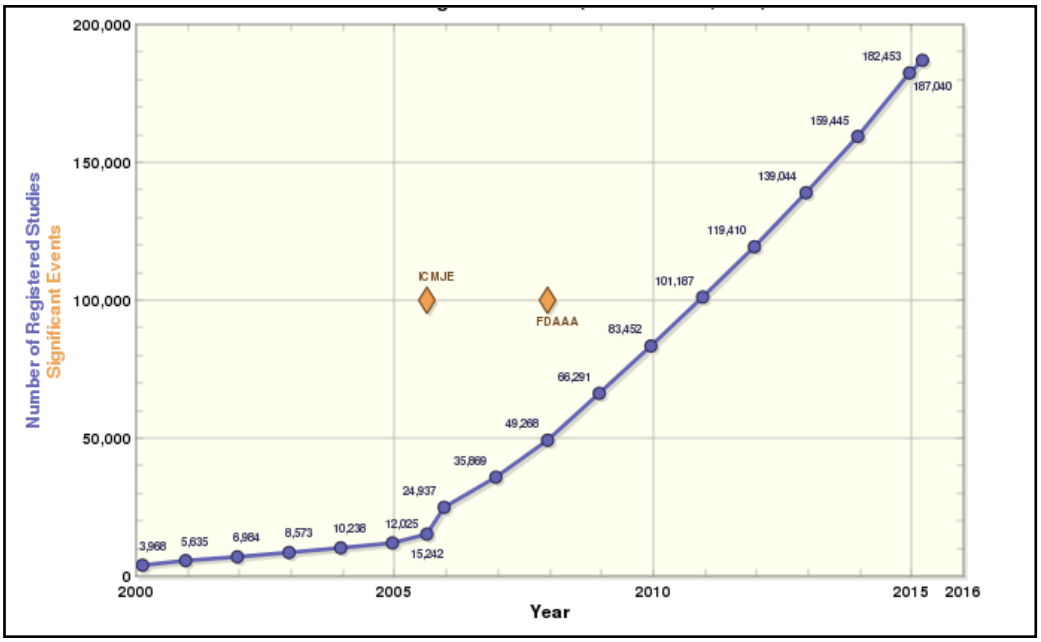


Location	Number of Recruiting Studies and Percentage of Total (as of March 26, 2015)
Non-U.S. Only	18,341 (53%)
U.S. Only	14,522 (42%)
Both U.S. and Non-U.S.	2,068 (6%)
Total	34,931

Source: *Trends, Charts, and Maps,* March 2015 (ClinicalTrials.gov 2015)

Figure 1.3

Number of Studies Registered to USFDA from Year 2000 to 2015



Source: *Trends, Charts, and Maps,* March 2015 (ClinicalTrials.gov 2015)

Note: ICMJE: Indicates when the International Committee of Medical Journal Editors (ICMJE) began requiring trial registration as a condition of publication (September 2005)

FDAAA: Indicates when the expanded registration requirements of Food and Drug Administration Amendments Act (FDAAA) began and were implemented on ClinicalTrials.gov (December 2007)

There is an exponential growth of clinical trials after the year 2005 and constant growth in number of registered studied till date (See Figure 1.3). There could be two reasons behind this exponential growth: one is different agency and acts i.e. International Committee of Medical Journal Editors (ICMJE) and Food and Drug Administration Amendments Act (FDAAA) made it mandatory to register clinical trials and hence researchers started registering their studies retrospectively (Doshi 2013). The other reason is outsourcing of the clinical trials to the developing countries satisfied the demand for the tremendous number of trial participants required for the clinical trials.

1.4.2 Globalization of Clinical Trials Industry in India

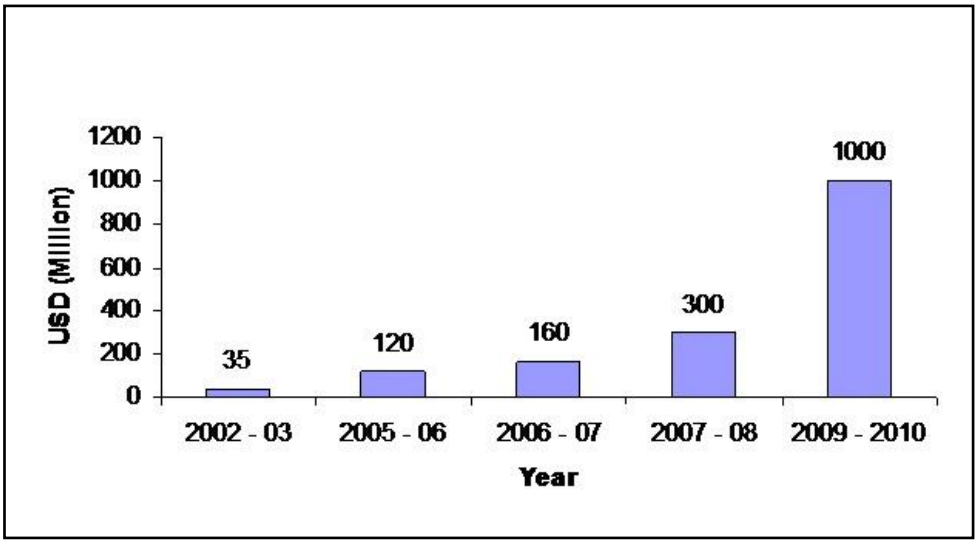
Till January 2005, clinical trials of new drugs being developed outside India were permitted only with a *phase lag* this means that a phase II trial was permitted only after completion of phase III trials elsewhere in the world. Phase I trials of foreign drugs were only allowed if, and only if, the drug is of special relevance to India or in a situation of an epidemic. This means phase I trial of Human Immunodeficiency Virus (HIV) was allowed because prevalence of HIV is very high in India and therefore it has a special relevance to India. This also means the phase I trial of Swine Flu vaccine would be allowed as there was a recent disease outbreak in India (Srinivasan and Nikarge 2009).

In January 2005, the Schedule Y of the Drugs and Cosmetics Rules was amended to remove phase lag clause in the act so that concurrent multicenter global clinical trials of multinational pharmaceuticals could be conducted in the India (MoHFW 2005). Phase II and phase III trials of drugs discovered in foreign countries could now be conducted in India in the same phase and at the same time as they are conducted in other parts of the world. The trial sponsor was now just required to get the study proposal approved by DCGI before starting a trial. For that they required to submit data from pharmacokinetic, animal studies, previous phase trials and informed consent documents only (Srinivasan and Nikarge 2009). Non regulation of clinical trials by state machinery along with other factors such as birth of trial conducting CROs and privatization of human research resulted in boosting of the confidence of the investors. The investments in clinical trial industry in India skyrocketed to almost

US$300 million at the end of year 2009 (See Figure 1.4). International reports also speculated that the Indian clinical trial industry will expand exponentially in coming years. For example, the McKinsey report estimated that clinical trial industry in India will be one billion dollars by 2010 (Sunder Rajan 2007). As per FICCI[6]-Ernst and Young Survey Report 2008, India could attract between five to ten per cent of the global contract research outsourced market over next five years (FICCI 2008 cited in Singh 2008).

Figure 1.4

Growth of Indian Clinical Trial Industry



Source: *Clinical Trials New Horizon-India* (Singh 2008: 7)

Note: Size of the market indicated in the year 2009-2010 is speculative

This resulted in over-flooding of the Global Clinical Trials (GCT) applications in the office of the DCGI which was not equipped to monitor clinical trials in India (See Table1.1 and Figure 1.5). Since year 2005, a large number GCT applications were submitted and processed for an approval in the office of DCGI (See Table 1.1). The data till 2009 shows that almost 770 GCT applications were processed for an approval. With limited man power, it was literally impossible for DCGI to inspect and audit clinical trial sites in India (Parliamentary Standing Committee 2012). On the other hand CROs were self auditing and certifying themselves for Good Conduct of trials.

[6] Federation of Indian Chambers of Commerce and Industry

Table 1.1

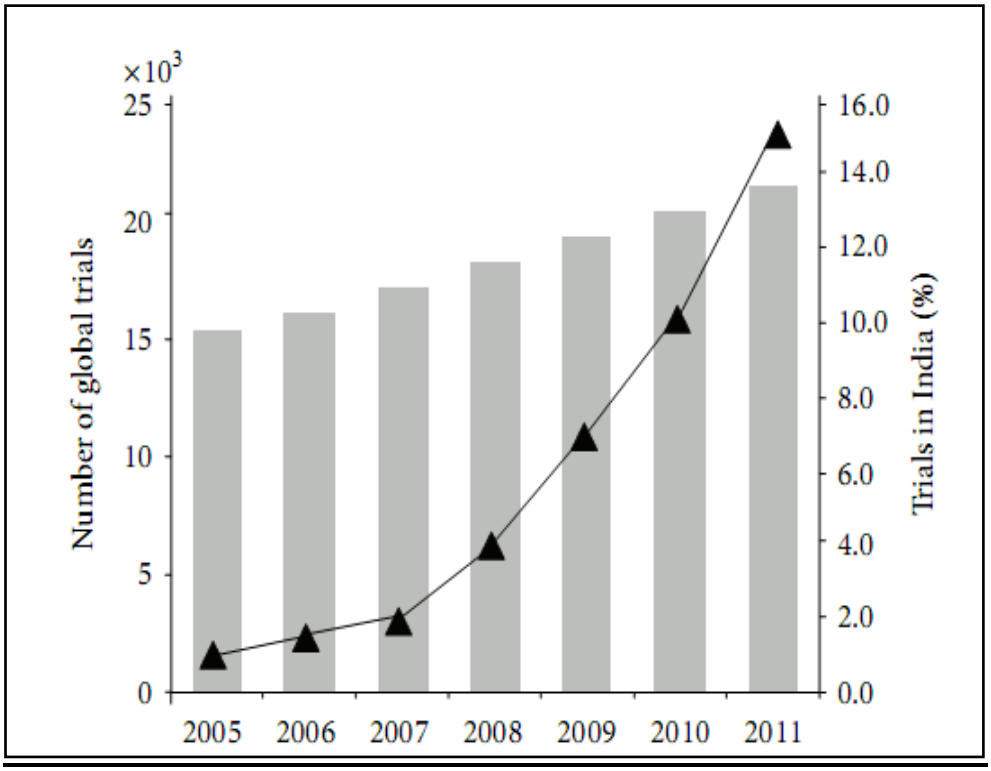
Number of GCT Applications received to office of DCGI

Subject	Applications Received in 2005 (Approx)	Applications Received in 2006 (Approx)	Applications Received in 2007 (Approx)	Applications Received from 2008 to 2009 (Approx)
Global Clinical Trials	100	170	200	300

Source: *Clinical Trials New Horizon-India* (Singh 2008: 19)

Figure 1.5

Number of Global Clinical Trials and the Proportion in India



Source: *Rise of Clinical Trials Industry in India: An Analysis* (Mishra cited in Bajpai 2013)

1.4.3 Trends of Clinical Trial Industry in India

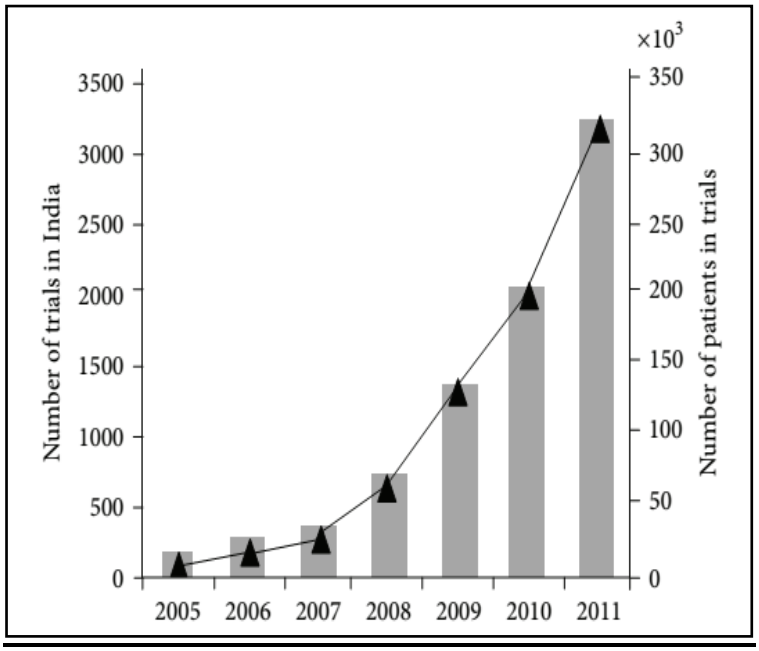
The whole trajectory of health service development in India involving the span of long decades started from the time of independence up to the development of large and unregulated private health sectors in twentieth century. If we consider the historical perspective of the health service development, then it can be described from inception of the Bhore committee, which envisaged the route map of the growth of health services of the population of the country mainly based on the robust foundation of the public health system through the responsibility of the state machinery. The committee attempted to formulate recommendations which not only gave emphasis for the deprived section of the society but also deftly built up the unanimous cognizance among existing political bodies about the state's responsibilities in the health sector and formulated some prescience steps such as recommendation of 12 percent of GNP for public health sector development of the country or encourage investment to develop sturdy public pharmaceutical sectors but it failed to tackle surging interest of the medical professionals at private level (Baru, n.d.). So the secondary as well as tertiary level of care took the major chunk of share of investment from the health service system. The whole structure has shaped the new notion of the health care in privileged classes of the society both in urban and rural areas. In 1973 first oil shock followed by the second oil shock in 1978 hammered the first nail in the dwindling public health service system in an indirect way (Baru n.d.). Those incidences trotted the whole world and many developing countries were suffering from the dreaded recession. Investment in public health sector was slashed down abruptly to combat that financial crisis (Duggal 2005). That vulnerable situation of public health service invited the capitalist forces to plant their private initiatives in the fertile land of health service sector. The new health services system emphasized its investment mainly in pharmaceutical, health insurance and different medical instruments and the process of medical equipments importation was sharply increased through the gross waiving of debt in importation of the medical instrument. In the early phase of health sector development, when the Bhore committee emphasized the self reliance of the country's own health service system over the multinational corporations, it was starkly noticed that in late nineties two giant investment bodies such as IMF and World Bank reshaped the investment pattern in the sector of public health service (Baru n.d.). The fatal period of recession

over the world in late twentieth century directed the trend of receiving loan to reform public health services through the adoption of the market principles. These principles did not limit itself only to the health service; it expanded its dark avenue to the ally of medical research, government health policy in different disease control programmes at country level. So the signatory membership of TRIPS was inevitable outcome for this country. As a result public health initiatives were overshadowed by the glorious presence of curative care at different levels across the country. it also has been observed that Secondary level of care became more prominent not only in large cities but also in outskirts and even in rural areas whereas the NRI controlled monopoly business of tertiary level care started ruling over the health service sector in large cities (Baru 1998) .

The private clinics, hospitals and Managed Care Organizations (MCOs) that emerged became the sites of the clinical trials with skilled man power and infrastructure. As already discussed earlier, after floodgates for the GCTs were opened up in year 2005, suddenly the number of clinical trials increased in India (See Figure 1.6). Indian clinical trial industry is dominated by phase III clinical trials at though numbers of trials of each phase are increasing. Substantial numbers of phase II trials are also being conducted in India which are *first in patient* trials and might be detrimental to patient's health.

Figure 1.6

Number of Trials and Patients in India



Source: *Rise of Clinical Trials Industry in India: An Analysis* (Mishra cited in Bajpai 2013b: 3)

Five states in India which are leading in the number of sites are: Maharashtra, Karnataka, Tamil Nadu, Andhra Pradesh and Delhi. In these states, numbers of private health organizations are flourishing which are also epicentres of the clinical trial sites. In five states where highest numbers of clinical trials are conducted, more than 50 per cent of the trials are conducted in Class A[7] cities of these states. The epicentre of the clinical research is also shifted from public to private sponsored research. Data indicates that around 83 per cent of the trials till June 2009 were sponsored by private organization (See Table 1.2). These private sponsors are mostly multinational pharmaceutical industries which wanted to conduct multicentre trials globally to fast track the trials and get marketing approval. The trend also shows that research in public institution is decreasing over the period of time while in private organization it is increasing. In India till June 2009, 75 per cent sponsoring organizations were non Indian. In this case it can also be observed that, sponsor

[7]Classification of cities or towns on the basis of 2001 Census (No.2(21)/E.II.(B)/2004).

organizations of Indian origin are decreasing over the period of time while sponsors of non Indian origin are increasing (See Table 1.2).

Table 1.2

Trends of Clinical Trial Industry in India

	Till 2003	2004	2005	2006	2007	2008	June 2009	Total
Phase of a trial								
I	6	3	3	5	4	7	3	31
II	11	11	26	28	43	41	12	172
III	46	34	54	105	123	120	28	509
IV	11	10	13	11	18	14	19	96
Sponsor Nationality								
Indian	23	19	26	34	32	34	20	188
Non-Indian	67	54	81	139	183	180	61	765
Indian and Non-Indian	13	6	11	10	11	11	4	66
Sponsor Ownership								
Public	28	12	16	21	17	21	12	127
Private	54	55	72	148	185	188	67	769
Non-profit	4	5	10	3	6	4		32
Top drug trial settings by states								
Maharashtra	50	46	87	206	197	226	37	849
Karnataka	29	42	76	122	141	175	23	608
Tamil Nadu	33	25	56	100	90	105	27	436
AP	23	28	60	103	110	100	21	445
Delhi	29	27	52	58	83	85	15	349
Top drug trial settings by cities								
Mumbai	33	31	54	101	99	103	12	433
Bangalore	25	34	57	83	99	118	15	431
Delhi	29	27	52	58	83	85	15	349
Hyderabad	21	27	47	79	81	73	16	344
Pune	13	15	28	71	71	73	13	284

Source: *Clinical Trials Watch* (Nikarge and Pamnani 2009: 228)

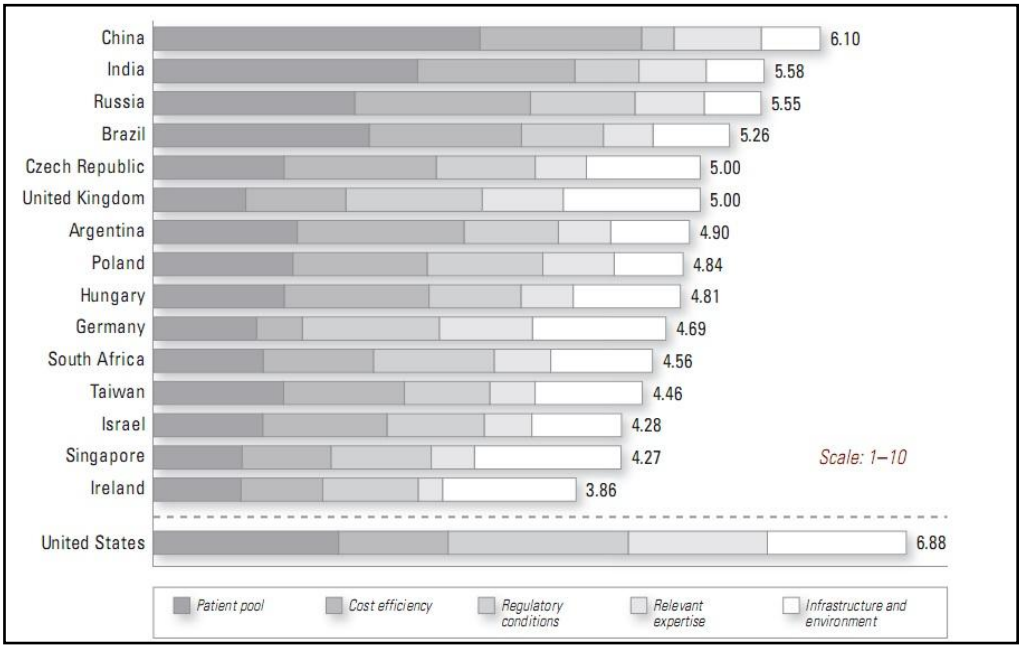
1.5 Factors Responsible for Globalization of Clinical Trials

There are number of reasons cited for the shift of clinical trial industry. These include minimum operational cost, a large pool of treatment naïve patients who can be recruited in a timely manner; the establishment of contract research organizations focused on global clinical trials; the rapid pace of growth of market size, research capacity and regulatory authority in emerging regions; and the harmonization of guidelines for clinical practice and research (Bailey et al 2008).

According to the Drugs Controller General of India (DCGI), India will be a preferred site for clinical trials because it has well equipped medical infrastructure and trained, English speaking human resource and it has *a large, diverse and treatment-naïve population with six out of the seven genetic varieties of the human race*; a pool of patients with both acute and chronic diseases, an increase in the number of patients with lifestyle disorders (Singh cited in Srinivasan and Nikarge 2009). Among emerging nations, China, India and Russia are the most attractive destinations to conduct the clinical trials (See Figure 1.7). Interesting to note here is except patient pool and cost efficiency, in all other indices, US is much ahead of India, China and Russia. Still, while calculating the average attractive index much of weight is put on patient pool (30 per cent) which leads to automatically increase in the average attractive index for three countries. This shows the desperation of the multinational pharmaceutical companies to target the patient pool from the emerging regions.

Figure 1.7

Overall Country Attractiveness Index



Source: *Make Your Move: Taking Clinical Trials to the Best Location* (Bailey et al. 2008: 58)

Note: Higher scores indicate higher levels of attractiveness. The 15 countries analyzed were selected based on size, diversity and geographical distribution. The index is not meant to be comprehensive across all potential offshore locations.

Another reason cited for the shift is to cater the needs of diseased people from developing world. It is said that due to clinical trials, the people from developing countries are getting access to advance treatments which are otherwise unaffordable. So it is interesting task to examine whether clinical trial industry is really responding to the needs of the people from developing countries. The critics of the pharmaceutical industry say that pharmaceutical products usually are of high cost and low relevance (Cottingham et al. 2014). The previous studies of the relationship between clinical research priorities and various measures of disease burden indicate that medical needs and drug development are disconnected from the needs of the global population (Trouiller et al. 2002).

According to the World Health Organization report the leading two causes of the mortality are the ischaemic heart disease and cerebrovascular disease accounting for 12.2 and 9.7 per cent of all deaths respectively. Also disease of lower respiratory infections and Chronic Obstructive Pulmonary Disease (COPD) are third and fourth

causes of the death worldwide accounting 7.1 and 5.1 per cent of total deaths respectively (Mathers et al). Given worldwide mortality rates, one would expect that the most needed drugs would be those developed to treat diseases of the circulatory[8] and respiratory systems. To study whether global clinical research is responding to the actual global burden of the disease or not, Cottinghem et al. did an analysis of the global clinical trial database. Their research findings, however, found a surprisingly small number of drugs under development for circulatory system disorders (5.93 per cent) and diseases of the respiratory system (6.78 per cent). Many chronic diseases also have limited drug development activity; although the most glaring drug development failures may be in the area of infectious diseases, responsible for more than 1,500 deaths per day. Neoplasms was the most common disease category targeted by drugs in the pipeline (26.2 per cent), followed by neurological and sense organs (13.48 per cent), infectious and parasitic diseases (10.5 per cent), and endocrine, metabolic, nutrition, and immunity (9.45 per cent). Complications of pregnancy (0.04 per cent), perinatal conditions (0.04 per cent), and congenital anomalies (0.24 per cent) were the least addressed in the clinical research. An even more surprising finding from their study was the over-representation of drugs in development to treat various types of cancer.

[8] Diseases of heart and blood vessels. Ischaemic heart disease and cerebrovascular are also circulatory diseases

Table1.3

Categorization of Trials by Health Conditions

Oncology	**Cardiology, Neurology, Nephrology**	**Diabetes**	**Major infectious disease or conditions**	**Common noninfectious conditions**[9]	**All other conditions**[10]
45 (9.9%)	89 (19.6%)	62 (13.7%)	TB: 6 (1.3%) GI infections: 3 (1%) RTI: 4 (1.4%) Malaria: 4 (1.4%) Total: 49 (8.6%)	50 (11%)	175 (38.6%)

Source: *Rise of Clinical Trials Industry in India: An Analysis* (Bajpai 2013: 14)

Perinatal conditions (46 per cent), respiratory diseases (22 per cent) and diarrheal diseases (10 per cent) are the top three causes of death in children in the India. On the other hand, cardiovascular disease (29 per cent), COPD and other respiratory diseases (10.2 per cent) and tuberculosis (10.1 per cent) are the main causes of death in adult age. If we analyze it in terms of the class, malaria, tuberculosis and malnourishment are the main diseases of the poor. The prevalence of malaria is three times higher, tuberculosis four times higher, access to antenatal care nearly four times lower, completed immunisation two times lower, rates of childbirth conducted by doctor four times lower, and malnourishment amongst women in reproductive age-group three times higher in the bottom one third of households (National Family Health Survey 2000). From the statistics available about Indian clinical trials, it can be said that that there is a clear disconnect between the disease burden in India and ongoing clinical research (See Table 1.3). It is not responding to the needs of the poor of the country.

[9]These included painful conditions (acute and chronic asthma, dyspepsia, indigestion, conjunctivitis, sore throat, common skin conditions, reproductive tract infections, depression, etc.).
[10] These included drugs used for all the other indications not covered by earlier categories.

Till now we have analyzed the claims of the clinical trial industry for the outsourcing of the clinical trials to developing nations. On the other hand we have to understand that globalization of the clinical trials is very complex phenomena and a number of factors were responsible for the outsourcing of the clinical trials.

1.5.1 Political Economy of Clinical Trial Industry

The major thrust to outsourcing was given by biotechnology revolution and advances in genetic engineering in the 1970s which resulted in a number of compounds that were coming out of laboratories, waiting to be tested for its therapeutic value. As former FDA Commissioner Mark McClellan said while addressing a meeting of researchers in 2003, 'There are more investigational new drugs, more experimental treatments today...than ever before' (McClellan cited in Shah 2006: 3). But the pace at which new drugs were coming out was far more than the capacity to carry out clinical trials and obtain FDA approval. As a result, there were tremendous delays before new drugs could enter markets. The reasons were obvious i.e. the process of experimentation of investigational drugs and producing reliable data is intensely time and resource consuming. For example, it costs around US$ 1500 to find, retain and successfully conduct one trial on one subject in a period of ten years. Apart from this, 85-90 per cent of drugs fail to show results at different phases of the clinical trials and hence do not obtain USFDA approval (Tonkens 2005). Thus there were many drugs clogged in the process of approval and that the industry started hunting for new grounds so that multi-centric trials could be conducted at a faster pace for the approval of drugs. Apart from the slow approval process, the unwillingness of US population to participate in the trials has also contributed to outsourcing. It is said that in order to develop a single drug, a drug company has to convince more than 4000 people to undergo 141 medical procedures each in more than 65 separate trials (Shah 2006). These numbers of people were simply not available in the US where less than one in twenty people were willing to participate in a clinical trial. In clinical trials of cancer medication, in which the industry offers trial participants the hope of getting a new treatment, it was observed that only less than four per cent of cancer patients were willing to participate (Shah 2006).

1.5.2 Clinical Trial Tragedies in Traditional Nations

Another possible reason for people in the US to be unwilling to participate in trials could be historical discrimination of people in clinical trial setup. The memory of coloured populations being unwittingly experimented upon is too recent to be forgotten. One example of such research was the historically infamous Tuskegee trial study which ended up in the deaths of a number of Black male participants because they were denied access to medicines during a course of trial.

In the Tuskegee syphilis study in the year 1932, the United States Public Health Service (USPHS) had initiated on experiment in order to investigate the natural history of syphilis untreated in Macon County, Alabama. The participants of the study were all Black men and the duration of the study was 40 years, the rationale of which was questioned later by an investigation panel. The study comprised of total 400 syphilitic Black men along with 200 non-syphilitic people in the control group. During the period of 1950s, penicillin was widely available for the effective treatment of syphilis. But access to penicillin was denied to all participant syphilis patients resulting in the death of almost 100 patients directly from advanced syphilitic lesions (Brandt 1978). Numerous articles, in both the professional and popular press, have pointed out that the study predisposed many African Americans to distrust medical and public health authorities and has led to critically low Black participation in clinical trials and organ donation (Ojanuga 1993). There was an impact of Tuskegee tragedy also on Human Immunodeficiency Virus (HIV) prevention and treatment programs (Thomas and Quinn 1991). The low enrolment numbers resulted in enactment of new legislative, such as the *NIHR*[11] *Vitalization Act of 1993*, which has a section titled *Inclusion of Women and Minorities* specifically addressing issues of women and people of Black communities and are given appropriate opportunities to participate in clinical trials research (Fisher and Kalbaugh 2011).

With stringent rules being set in the US, the large population in emerging markets like India and China are seen by the pharmaceutical industry as potential sites for clinical research. As one of Pfizer press release says ‘apart from the low-cost of field

[11] National Institute of Health Research

trials, a billion people means there is never a shortage of potential subjects' (Shah 2006: 8).

1.5.3 Privatization of Academic Institutions

Till the period of 1970s, most of the trial centres in the US were university hospitals and academic doctors were the principle investigators. There were several benefits of conducting trials in university hospitals because doctors there had trial design expertise, a pool of patients were also available and the trials were conducted independent of sponsorship by pharmaceutical companies. But after the 1970s oil shock and economic depression, the US economy was reorganized on the line of innovation based industry. It resulted in tremendous investment in the field of research such as ecology, biotechnology, genetically modified crops which claimed to provide solutions to limits of the growth (Cooper 2008). The venture capitalist who were initially investing into the manufactured industry, also realized the limitations of the Fordist model of economic production (Sunder Rajan 2006). Now venture capitalist also believed on the potential of innovation based economy and therefore invested in the research and development of innovative technologies. The field of biotechnological research also reorganized itself in line with new types of science and technology and changes in the legal, regulatory and market structures (Sunder Rajan 2006). The supportive legal climate for the biotechnology research was created by enactment of the *Bayh-Dole Act, 1980* (Inda 2014). It facilitated the transfer of technology between academic institutions and industry. Following it, in a landmark ruling of US Supreme Court in a case of *Diamond vs. Chakrabarty*[12], it was allowed to patent genetically engineered microorganisms (Sunder Rajan 2006). The new techno-science of recombinant DNA technology (RDT) was discovered through which it was now possible to cut and join different Deoxyribonucleic Acid (DNA) molecules. The life sciences hence transformed as a techno-science and the product of this process were the DNA or protein. It was also predicted that some of these proteins could have therapeutic value and be industrially produced. This resulted in many drug molecules which were to be tested for its therapeutic value. As

[12] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), was a United States Supreme Court case dealing with whether genetically modified organism capable of breaking down crude oil can be patented or not.

drug market skyrocketed in the 1990s, drug companies wanted a faster delivery of results of the trial. As noted by Thomas Bodenheimer of University of California, 'Pharmaceutical firms are frustrated with academic medical centres' (Tomossy and Weisstub 2003: 514). It was also the period when privatization of the universities resulted in hijacking of clinical research from universities and publically funded laboratories by giant biomedical private industries in the US. According to Health Care Financial Management Association's newsletter, twenty years ago 80 per cent of clinical trials were conducted in academic medical centres which has dropped now to less than half (Sunder Rajan 2007). This transition had changed the way trials are being conducted (See Table 1.4).

Table 1.4

Fundamental Difference between Academic and CRO Research

Academic Research Centers	Contract Research Model
Trial Design Expertise	No trial design expertise
A patient population from which to draw sample	Speeding up clinical trial and profit making
Prestige and publishing research	Authority of pharmaceutical companies over produced data

This transition of the clinical trial had many serious repercussions. According to it, the principle investigator conducting the trial did not require to have expertise in the area of research. There was transition in the role of researcher from the 'scientist' to 'manager' of the clinical trials. The emphasis now was on speeding up the trial. It is not the researcher but the pharmaceutical company that exercised control over the data generated. As a result, this increased the chances of manipulating of the data in favour of the company by not disclosing Severe Adverse Events (SAEs) and deaths (Fisher and Kalbaugh 2012). All these factors culminated in a state when in 1987, USFDA started accepting data from clinical trials conducted outside the US and indeed, to accept a new drug application with data solely from non-US trials (Shah 2012). Now companies need not take FDA approval before conducting trial on non-US patients. Further, USFDA was no more tracking the research. This move then channelized outsourcing of clinical trials to other developing countries like India, China and Brazil.

Table 1.5

Year wise Breakup of Sponsor Profile Trials in India

Sponsor Profile	Year Missing	2003 and Prior	2004	2005	2006	2007	2008	June 2009
Institution or Agency	11	59	28	45	47	46	43	19
Pharmaceutical	5	43	49	68	136	177	178	64
Both		1	2	5				
Sponsor profile not known	5							
Total	21	103	79	118	183	226	225	85

Source: *Clinical Trials Watch* (Nikarge and Pamnani 2009: 228)

This model of transformation from publically funded university hospital trials to private industry owned research in Contract Research Organization (CROs) was replicated in all developing countries, including India. The institutional research gradually started decreasing while pharmaceutical industry sponsored research increased rapidly in India (See Table 1.5). The model of the outsourcing of the research to CROs, competition within CROs to attract more sponsors and give them instant results have its negative implication on the rights of the patients and trial participants.

1.5.4 Cost and Time Efficiency

As clinical research was ready to take off from tradition regions, developing countries were making grounds in terms of less regulation and minimizing costs in order to attract the clinical trial business. Time and cost are inversely related in clinical research. If clinical trial of molecule is delayed, the cost of conducting clinical trial increases. Once industry discovers one molecule, it is very hard to maintain its secrecy while conducting clinical trials. Hence drug companies usually acquire patents of the molecule before the actual clinical trial starts (Bajpai 2013). The duration of patent granted to molecule under Trade Related Intellectual Property

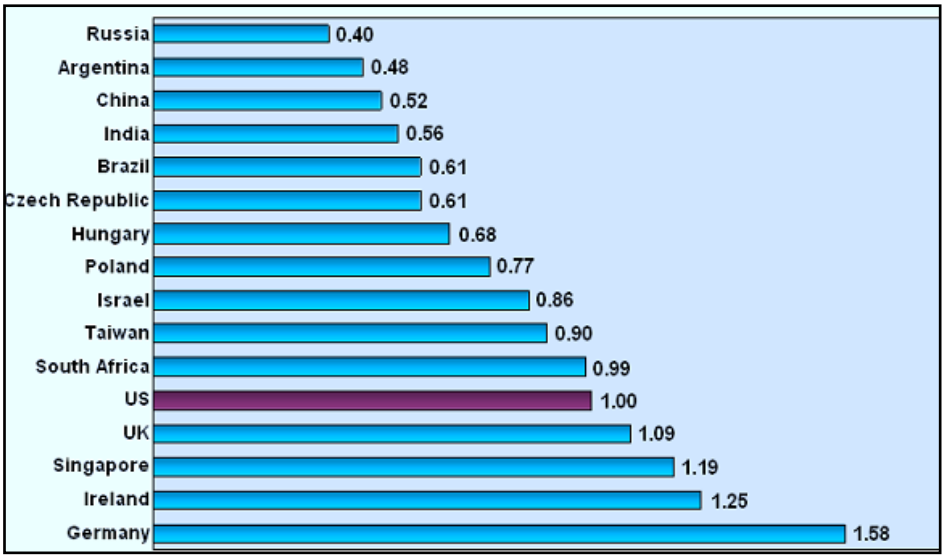
Rights (TRIPS) is 20 years. It usually takes around two to twelve years and it cost $1.8 billion to complete all phases of clinical trials and take approval for marketing (Tonkens 2005). The cost claimed in this source is questionable as the cost of research and development of a drug is always a secret affair of the industry. The time for drug development is a matter of concern. A substantial part of the 20 years patent period is lost in the clinical trial phase. Hence the industry strives to reduce this time so that it gets the maximum time to exploit the molecule commercially before its exclusive rights over the molecule expires (Bajpai 2013). The globalization of the clinical trial is one strategy adopted by industry to fast track the drug development process where it is allowed to conduct multi country, multi centric clinical trials in order to satisfy scientific norms constituted. Apart from this, the phase lag removed lead to transfer of phase III trials, which require a large sample size, to the developing world. Hence pharmaceutical industry usually seeks optimizing costs of clinical trials by getting fast approval for clinical trials, conduct clinical trials with low costs and launch drug with a patent in the market. These criteria are satisfied by conditions in developing countries. In a conference organized by Fortis Healthcare in India it was stated that, 'India also offers significant cost advantage as compared to developed and other emerging economies, 40-60 per cent lower than in developed countries and 10-20 per cent lower than emerging economies (EH 2015: 2). Apart from this, depending on the choice of location, cost savings can range from 30 to 60 per cent compared with sites in the United States or Western Europe (Bailey et al. 2008). The statement given by one of the Investigator from Bangalore in a qualitative study conducted justifies it.

> If you conduct a phase 1 clinical trial in the US, it will cost you around $25,000 per case. But if you do the same study in India, we can do it for less than $1000 per patient. So the best thing about India is the low cost, and the treatment cost and consultant cost; everything is very accessible because of the high patient pool (Kamat 2013: 51).

Actual conduct of the clinical trial includes expenses under different heads which includes manpower, rental, IT and operational costs. We can see that overall cost of Brazil, India and China is almost half as compared to the US.

Figure 1.8

Overall clinical trial cost in different countries



Source: *FDA Perspective on International Clinical Trials* (Ayalew 2013: 10)

The reasons for this cost differences are many. The compensation offered is comparatively low, personnel costs are very low as compared to the US and regulatory and beaurocratic costs are also low.

Table 1.6

Comparison of Drug Approval Process

Country	Time for Evaluation of MAA	MAA Fee in USD
Australia	50 days	192,400
China	180 days	DNA
India	8-12 weeks	786.78
UK*	210 days	396,396
USA	180 days	217,787

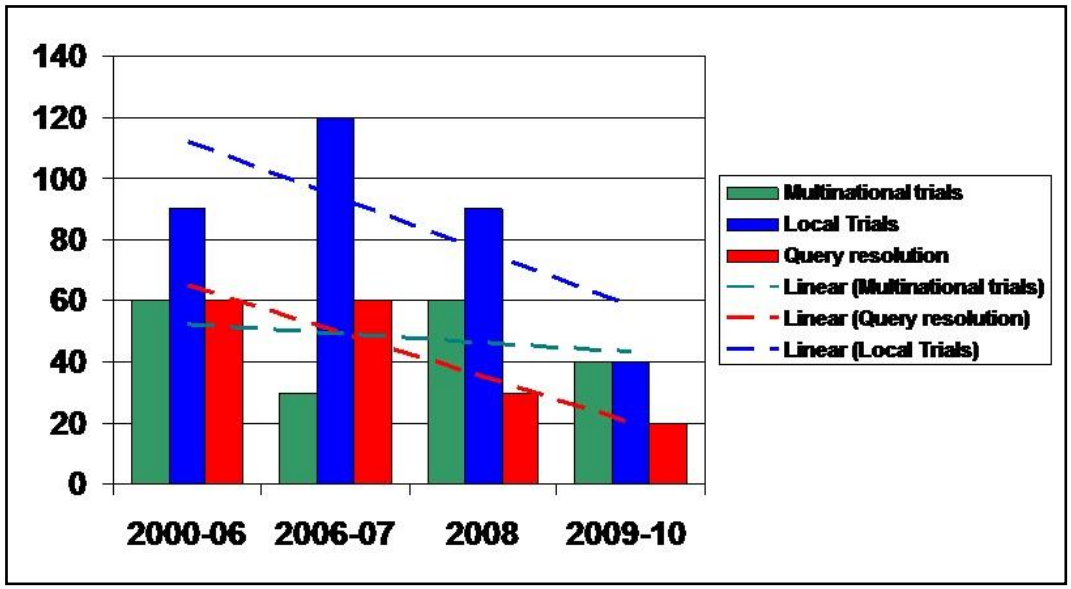
Source: *New Drug Approval Procedure in India* (Patel et al. 2012: 2)

Note: MAA-Marketing Authorization Application, DNA-Data Not Available.

Apart from this, companies try to save cost through fast tracking the approval for trials (See Table 1.6). It is one of the crucial phases of the clinical trial is a phase of regulatory approval. The data related time required for regulatory approval Marketing Authorization Application (MAA) shows that emerging countries take very little time compared to traditional countries. According to another study, in emerging countries, pharmaceutical companies can complete Phase III trial up to six to seven months sooner than in traditional sites (Bailey et al. 2008). The regulatory authorities in India are partial towards approving proposals of multinational (See Figure 1.9). But the crucial factor is cost and that is very much less in developing countries which are emerging grounds for clinical research. The processing fee of the MAA is also very less in the emerging regions as compare to traditional regions.

Figure 1.9

Clinical Proposal Review Timelines



Source: *Clinical Trials New Horizon-India* (Singh 2008: 7)

1.5.5 Contract Research Organization: A Liability Organization

Traditionally clinical trials were conducted mainly in the academic institutions. However with growing existence of multinational pharmaceutical industry and number of drugs to be tested in the pipeline demanded recruitment of larger pool of

patients for diverse number of disease. Additionally these pharmaceutical industries do not have direct access to the patients as well as doctors who can be Principle Investigators (PIs) to conduct the trials. At the same time, Indian pharmaceutical industry which was into a production of generic medicine got setback after the enactment of the *Patents Amendment Act, 2005* which abolished the process patents in India. As discussed by Kaushik Sunder Rajan (Sunder Rajan 2007), the ratification of the product patent by the Indian government in 2005 lead to loss of Indian pharmaceuticals who were manufacturing patented drugs with different processes and marketing. This change forced these industries to jump into research and hence they also started promoting the clinical trial industries. This entire context demanded the need of a specialized organization which can perform the task of research in drug development, recruit required number of patients and produce reliable data out of clinical trials. These organizations are called Contract Research Organizations (CRO) to which pharmaceutical industry contracted out their research task. These institutions were the link between Multinational Pharmaceutical Companies (MPC) who wanted to conduct the trial and principle investigators seeking profit. The complexity of organising trials in developing countries, and about reporting and managing them, led MPCs to push for the establishment of CROs. One of the data manager who works in one of the CRO in Mumbai expressed in a informal interview[13] that,

> Actually CROs are liability organizations, means none of the stakeholders i.e. either pharmaceutical industry or principle investigator wants to take liability of either SAEs in participants or reliability of the data. That is why we came in. We do take care of everything i.e. recruitment, retention, managing SAEs if there any and producing data which pharmaceutical industry want (CRO Executive, January 2015)

Limited availability of the patients and phase I participants who fits in the inclusion criteria of the study is always a biggest challenge in front of the CROs. Hence CROs usually end ups in manipulation of the data in order to achieve the sample size of the study. The reliability of data produced by the CROs is questioned by a number of clinical trial investigation agencies. In a recent case of Hyderabad based CRO called GVK Biosciences, the European Union (EU) suspended 25 drugs after it was realized that the data produced by the GVK was flawed (EU Suspends GVK Biosciences

[13] He is a researcher's friend working in one of the CRO from Mumbai and gave an informal interview to the researcher in January 2015

2015). According to investigation by French medicines agency, it was found that data related some Electrocardiograms (ECG) was manipulated during trials. In another incident, World Health Organization (WHO) found critical flaws in the trial of HIV drug conducted by Quest Life Sciences. The WHO investigation team said that, 'Subject detail...and dates had been changed by the company, in the majority of cases, to make the ECGs appear as if they were from each of the different subjects' (After GVK Biosciences 2015). This trend has a serious implication because the CROs which are purely working with profit making motive. They are more interested in completing more and more studies and earn profit rather than producing reliable data.

1.5.6 Speculative Reports by International Consulting Agencies

The positive speculations of consultancy firms and various governments boosted the confidence of investors and led to the rapid expansion of the clinical trial industry. Many consultancy firms published their reports citing the benefits of conducting clinical trials in emerging nations. They also tried to build the trust of investors by speculating on the profit potential of the Indian clinical trial industry. For example, McKinsey report estimated that clinical trial market in the country would be one billion dollars by 2010 (Singh 2008). Ernest and Young predicted an even higher potential of the market at around US$1.5-2 billion by 2010. Even the government agencies joined speculative market predictions to invite the investors. For example, according to report of the High Level Group on Service Sector of Planning Commission of India, the estimated market value for clinical trials outsourced to India was around US$300 million. With an estimated growth of 65 per cent per annum, they even predicted that the clinical trial market in India would touch US$ 1.5-2 billion by 2010. But the ground reality was very different. While a clinical trial sector was emerging in India, the infrastructure and human resources were still not in place. Notwithstanding the hype created around the potential growth of clinical trial sector in India, the actual investment in the industry reveals a different story. The Managing Director of a CRO sums up the ground reality in the following statement:

> When I first took this job, everyone was saying, "Oh yes, we are going to be a one billion dollar industry by 2010"but where is all the money that we have been talking about? At least I haven't seen it! I would like to do many more trials, but there are not many companies that are keen to come to India (Kamat 2013: 51).

Another noticeable fact is that, in 2006, less than one per cent of the commercially sponsored global clinical trials were being conducted in India (Bailey et al. 2008). In 2007, there were only 757 sites in India with a trial density of 0.7, as compared to 36,281 sites in the US, with a trial density of 120.3 (Kamat 2013). Hence we can safely conclude that these speculations were deliberately aimed at attracting investments and pushing the Indian government to enact laws favouring the clinical trial industry. The basic purpose of this speculative market was to boost the confidence of the investors, especially venture capitalist, to invest in the clinical trial sector in India.

1.5.7 Government Working at the Behest of Pharmaceutical Industry

At a meeting of the Institute of Clinical Research [India] in Mumbai, Surinder Singh, Drugs Controller General of India, described a number of other steps that the government was planning to undertake in order to promote the clinical trial sector in India. In addition to changes in the *Drug and Cosmetic Act, 1940*, a single window clearance for clinical trial applications was offered in order to reduce the approval procedure to between two and six weeks. DCGI also promised in this meeting that *Category Protocols* which consist of protocols from the US, United Kingdom (UK), EU and Japan would get fast track approval of six to eight weeks as against Category B trials from other countries which would get approval in eight to 12 weeks (Srinivasan and Nikarge 2009). He also said that the government would grant a license to import supplies within two weeks of the application being made. The DCGI also promised that the local EC review would be completed in six to eight weeks. On top of that, the Indian government also projected its support to clinical trial industry by providing *tax holidays* to these companies (Kamat 2013). DCGI lifted the import duty on clinical trial supplies and promised that permission for export of clinical trial specimens would be granted at the same time as the protocol was approved by the DCGI. Clinical trials were exempted from sales tax also (Srinivasan and Nikarge 2009).

The other contributory factors were India's compliance to the product patent regime in 2005 along with guaranteed patent protection under TRIPS agreement. After being a leading player in Information Technology, the aspirations of becoming a global player in biotechnology, in competition with China, also contributed in encouragement and creation of the legal environment (Sunder Rajan 2007). It was not a coincidence that the year 2005 also saw the enactment of a range of legislation in favour of the pharmaceutical industry in general and clinical trial sector in particular.

Table 1.7

Resource Advantages as Destination for Clinical Trails

Stakeholder	Characteristics
Investigators	Large number of specialists in different therapy segments
	Medical training in English
	600,000 English speaking physicians
	PG[14] training from Europe/US
	Treatment protocols in line with the West
	Large number of GCP complaint investigators/sites
Patient population	Large, diverse, therapy-naïve
	Advantage of having six out of seven genetic varieties
	Large patient pool in acute/chronic disease segment
	Increasing number of patients in life style disorders segment, HIV, oncology
Clinical research Infrastructure	Over 200 medical colleges
	Over 22,000 graduates per year
	15,622 hospitals, 903,952 beds (more than 75 % in urban area)
	14000 diagnostic labs
	700,000 scientists and engineering graduates/year
	World class medical/lab facilities at secondary/tertiary care centers
	Skilled computer savvy biomedical work force
IT support	Highly developed IT[15]/ITES[16]
	Motivated and committed personnel
Connectivity	High quality digital connectivity
	Excellent air/surface transport facilities across country

Source: *Clinical Trials New Horizon-India* (Singh 2013: 12)

[14] Post Graduate
[15] Information Technology
[16] Information Technology Enabled Services

Table 1.7 clearly indicates how the DCGI was marketing the India's vulnerable and *treatment naïve* population to the multinational pharmaceutical companies. What emerges here clearly is that the India state has abandoned the role of providing welfare services to its people in favour of investment maximization i.e. India.Inc[17] (Sunder Rajan 2006).

Another evidence of state acting at the behest of the pharmaceuticals was the 59th Parliamentary Committee report, presented in the Parliament on 8th May 2012 on the *Functioning of the Central Drug Standard Control Organization (CDSCO).* The report pointed out that at the very outset the CDSCO being the apex body and assigned the task of regulation of drugs, it should protect the interests of consumers. But its stated mission, '*to meet the aspiration of pharmaceutical industry'* is skewed and it ignores the interest of the largest group, that is, the consumer (Parliamentary Standing Committee 2012). It goes on to describe in detail the structure and function of the CDSCO and the gaps therein. According to this report, CDSCO seriously lacks in infrastructure especially trained human resources to discharge its functions effectively. While India wants to become a global leader in medicines, there are wide gaps in the qualification requirements of the head of CDSCO, that is, the Drug Controller of General of India (DCGI), as compared to the developed countries. In India the academic requirement for the post of DCGI was merely a graduate with Bachelor of Pharmacy (B.Pharm) degree (not even MD pharmacology). The heads of the drug regulation departments of US and UK are persons of wide experience and qualifications. The *New Drug Division of* the CDSCO has neither adequate number of trained staffs to handle flood of applications nor a transparent institutional mechanism to obtain expert opinion. Further there is no time schedule for processing and disposal of applications received (Parliamentary Standing Committee 2012).

The Committee randomly selected 42 medicines from the list of new drugs in order to scrutinize the approval process of new drugs. They found that the files of three new drugs were not traceable. All the three drugs were controversial which had been discontinued in western countries but were approved for marketing in India. After scrutinizing the files of rest of the approved drugs, the committee came up with a list of very serious violations such as approvals were granted without conducting

[17] India Incorporation

mandatory trials or seeking expert opinions and wherever the opinion was sought it was mostly orchestrated. The DCGI approves on an average one drug per month without trial. The DCGI approved 33 new drugs between January 2008 and October 2010, without conducting trials in India ostensibly to address public interest in the context of challenges posed by serious diseases. But CDSCO did not even bother to pay attention to post marketing surveillance, for drugs might have different responses in persons of different ethnicity. The CDSCO miserably failed to seek expert opinion in at least 28 cases of new drug approval. The committee gave the example Buclizine a drug for increasing the appetite in children. The drug, which was banned in many countries including the country of its origin i.e. Belgium, was approved in India without any trial. The Committee alluded to the dangerous nexus between pharmaceutical companies and expert doctors by pointing out the defective process of seeking expert opinion. One of the striking observations of the Committee was that there was uniformity in the letters drafted by different experts for marketing approval of medicines without trials. The fact that the letters for approval from different parts of the country reached the DCGI office on the same date led the Committee to conclude that they were collected by the interested parties (Parliamentary Standing Committee 2012).

The Committee also argued that the trials in India are conducted in a haphazard way for just sake of marketing approval of drugs. In order to justify its observations the Committee gave a number of examples. One such example was of Letrozole. Although Letrozole is used in the treatment of female fertility, it has not been permitted for use in women of reproductive age. However, in India, skipping phase II trial, only phase III trial was conducted on merely 55 women in three private clinics to approve the medicine for marketing. The phase III sample size was insufficient and India was only country in the world to approve this medicine for marketing. Later, however, the Health Ministry had to ban Letrozole owing to public and media pressure. Nevertheless during the short period when the drug was in the market, company made huge profit and no action was taken against the CDSCO official who had approved the medicine without following due procedure (Parliamentary Standing Committee 2012).

Hence the Committee concluded that the drug regulatory system in the country is not up to the required standard. It has poor infrastructure and is unable to discharge its

function of regulation. It carries out approvals in a non-transparent manner promoting the interest of pharmaceutical companies rather than that of consumers.

1.5.8 Principle Investigators: The Agents of Pharmaceutical Industry

In a country like India where regulatory mechanisms are not developed and are still evolving, concerned authorities need to be extra cautious in sanctioning large number of clinical trials. 23 out of 30 states in India lack of proper mechanisms for the registration of private hospitals and nursing homes (clinical establishments), yet the CDSCO is giving permissions to conduct clinical trials in the private institutions in these states (Ministry of Law and Justice 2010). In 2011, the Economic Offence Wing (EOW) of Madhya Pradesh investigated 81 trial subjects and found serious allegations of lapses in the regulatory framework.

This clearly indicates that regulatory mechanisms are not in the place. However, in a context where states are following neoliberal policies to attract foreign investments, they themselves are in a vulnerable situation in relation to foreign corporations they are trying to woo. One way of wooing foreign capital is to have weak regulatory regimes. In this race of profit making, doctors as principal investigators also compromise on ethical principles. The role of the doctors as Principle Investigators (PI) is very important because they are directly in contact with trial subjects and hence able to take decisions in their favour. But the evidences show that the doctors often collaborate with the pharmaceutical industries. During the period of neo-liberal economic reforms, health services in India started emulating the US's model of privatized MCOs. Many Indian states allow physicians, who are working in the government hospitals to also carry out private practice. This along with their profit maximisation and association with MPCs, has led to several cases of fudging of data generated during the clinical trial in favour of the pharmaceutical companies (Fisher and Kalbaugh 2012). The 59th Parliamentary Report on the functioning of the CDSCO also alludes to CDSCO-doctors-pharmaceutical nexus because drugs have been approved for marketing in India without clinical trials (Parliamentary Standing Committee 2012). We can safely conclude that there is a clear alliance between doctors and MPCs through CROs. A qualitative study also shows that one of the prime motivations for doctors to conduct clinical trials was financial incentives

(Kamat 2013). Another important factor is passage of *The protection and the utilization of the public Funded Intellectual Bill, 2008* inspired by US's *Bayh Dole Act*. This encourages the researchers working in the government institutes to claim intellectual property rights over their invention. The table below shows the incentives gained by five doctors in Madhya Pradesh conducted trails in the government hospital using public resources.

Table 1.8

Money Revived by Each Doctor through Clinical Trials, Indore, Madhya Pradesh

Sr No	**Names of Doctor**	**Designation**	**Amount received from Drug Trail-Based on EOW report**
1.	Dr Anil Bharani	Professor, Dept of Medicine,	1.53 crore
2.	Dr Salil Bhargav	Professor, Chest and Tb, Superintendent, M.Y Hospital	1.05 crore
3.	Dr Pushpa Verma	Professor and Head, Dept of Ophthalmology, Dean, MGM medical college	0.08 crore
4.	Dr Hemant Jain	Professor, Dept of Pediatrics	1.70 crore
5.	Dr Ashok Bajpai	Ex Professor and Ex head of Dept of Medicine, Ex Dean MGM medical, owner of Rajhshri Hospital, Vijay Nagar, Indore	0.48 crore
6.	Dr Apoorva Puranik	Professor , Dept of Medicine.	0.26 crore
		Total	**5.10 crores**

Source: *Economic Offence Wing Report* 313-5/11 (EOW 2012: 8)

Note: This information has been revealed in the EOW investigation report and report is in public domain.

1.5.9 Expropriation of Treatment Naïve Bodies

The availability of a large number of treatment naïve subjects willing and eager to participate in trials is another favourite reason given by the pharmaceutical industry for generation of the reliable data. One assumption is that the majority of people in developing countries do not have access to modern medicines and hence relative presence of treatment naïve population is more in developing countries. This assumption does not stand the scrutiny of empirical evidences for many patients in India prefer because they usually self medication as primary treatment measure. A study conducted by Lybrate, India's doctor-patient end-to-end communication platform found that 52 per cent of Indians indulge in self medication (Perappadan 2015). The absence of public health services and unaffordable private health service force people to choose self medication. The advocates of unfettered clinical trials in India claim that people are eager to participate in clinical trials. Studies have indicated that people usually participate in clinical research because of following reasons: they want to help advance medical knowledge, they want to access promising treatments, and finally, the monetary benefits it brings (Fisher and Kalbaugh 2012). The current paradigm of clinical research lures participants by monetary benefits. This has become a major issue in developing countries where majority of the people do not have access to health services. Also, because of prevalent unemployment and poverty some people are falling prey to the lure of compensation and the monetary benefits they bring.

The pharmaceutical industry treats the poor and malnourished, who do not have access to health care services, as resources to accrue profits. In *Capital*, Marx shows that this availability is generated by pre-existing acts of violence that created a property-less proletariat (Sunder Rajan 2007: 84). Capitalism converted pauperised peasants into proletarians in the West. They were forced to migrate to cities to fulfil the demand for labour in the industries. They were *freed* from their attachment to the rural economy to be exploited in the industrial sector. In the Indian case, under-employed and unemployed populations are now *free* to transact their bodies. In this context, Kaushik Suder Rajan argues that there is structural violence where it acts not directly through violence but through social and economic forces which compel an individual to participate in a clinical study to mitigate future violence of poverty and hopelessness.

1.6 Summary

Although the leading capitalist economies are the still epicentre of the clinical trials, there is tremendous growth of clinical trials in emerging nations such as India, China and Russia in recent years. Several push and pull factors played a major role in the globalization of the clinical trials. The tightening of regulations in the traditional countries following several clinical trial tragedies, cost and time efficiency in conducting trial in emerging countries, privatization of clinical research, emergence of the CROs and doctors in developing countries with profit making motive were some of the important factors contributed in globalization of clinical trials.

The over-flooding of clinical trials of NCEs has a severe impact on India following the amendments in the Drug and Cosmetics Act. The clinical trials conducted in India are mostly sponsored by private pharmaceutical companies; urban centred; conducted in the private clinics and people from marginalized section are the targets of the clinical trials. Several laws and rules have been flouted while giving approval for the clinical trials and also during the conduct of the clinical trials. The lack of regulation of clinical trials has resulted in the number of SAEs and deaths and they are denied compensation. On the other hand, doctors, CROs and pharmaceutical companies have made a good amount of money through the conduct of clinical trials.

Chapter 2

Clinical Trial Tragedies in US and India

2.1 Introduction

Historically, the marginalized communities from different parts of the world have been exploited based on race, caste, class and gender. For example, in the United States (US) the African American exploited based on race, class and gender while in India the caste, class and gender were dominant means of social, economic and political exploitation. In the United States (US), the European White settler population perpetrated violence on indigenous population in order to grab their land for commercial production. Further, the need of deficient labour was met by importing slaves from African colonies. Since then, the exploitation of these marginalized communities is going on in the different parts of American continent. In India the caste, gender and class are systems of exploitation. They have stratified different social groups at different levels based on their work and socioeconomic status. The people of these groups have been socially and economically exploited throughout history. Same is the case of tribal population in India which was geographically untouchable. When the British acquired the territories in the Indian subcontinent, they also aligned with existing power structures to fulfil their economic interests. Even after independence, little changed; and measures like land reforms and social justice have mere mirages for these communities. Since the early 1990s, when the processes of globalization began in India, these exploitative structures have been reinforced through more economic exploitation and alienation of the marginalized population. The rift between poor and rich has only increased and more and more people have been dispossessed even of means of subsistence. These exploitative characteristics have been percolated in every institution, whether private or public. This chapter tries to examine the history of exploitative characteristics of clinical research institutions in the US and in India and its influence on the current clinical research regime.

2.2 Clinical Trial Tragedies in US

In the initial years of European colonization of the North American continent, the White indentured labour imported from Europe was a source of workers to work in the vast and harsh fields of tobacco (Slavery in the United States 2014). There was critical shortage of labour because working conditions were harsh, labours had to be import from Europe and their master had to pay the cost of the travel and food. In the early seventeenth century, Dutch colonizers introduced the institution of slavery when they charted a number of ships transporting African Black people to work in their tobacco fields (Slavery in the United States 2014). When cotton replaced tobacco as the main cash crop in the nineteenth century, the southerners[18] became more exploitative and coercive in order to extract more work at cheap costs from slaves (Slavery in the United States 2014). Punishments by whipping and other kinds of torture, and, the splitting up of the families by sale of members to different masters are some of the sufferings of the slaves (McQueen 2013). The Civil War out broke in the mid nineteenth century between the Northerners[19] and Southerners. The Northerners were fighting to preserve the Union and were against the institution of slavery. After the end of the Civil War, the US adopted the 13th Amendment to the constitution which completely abolished the practice of slavery. Although Northerner Whites were against the practice of slavery, they endorsed the view that Black people were inferior to the Whites (Slavery in the United States 2014). This racism has continued to shape US as evident in a number of incidences of discrimination against African Blacks.

2.2.1 Human research in the Antebellum Period

The field of human research and medicine never remained untouched by racism. The unscientific rationale and propositions of research were a reflection of prevalent ideologies regarding race and heredity in the early twentieth century US. Hence, before examining the racism's historical relation with biomedical research, let us first explore the dominant scientific ideas regarding race and hereditary in the early twentieth century. In 1859, Charles Robert Darwin published his work *On the Origin*

[18] Southerners were people from south US who seceded from USA and formed their new nation.
[19] Northerners were called Union or United states who remained loyal to the Federal government.

of Species on biological evolution and natural selection. Darwin's theory of natural selection was adopted to rationalize the already existing racism of the White American population. Social Darwinists argued that the primitive Black population cannot assimilate with the superior White race and will go extinct. With an analysis of the birth registers, they tried to show that African American have high fertility rate and hence are over-breeding. But at the same time, they attributed the decreasing in the Black population to the inferiority of Black population (Brandt 1978). They argued that, this primitive community is on verge of extinction and even with the provisioning of social services like health, education and food could not alter extinction process. Several studies during this period claimed that the primitive Black population was more prone to disease, vice and criminality and were therefore incapable of becoming part of civilisation (Brandt 1978). The medical profession also embodied these dominant tendencies and dehumanized and animalized African American people. This was evident, for example, when they institutionalized a comparative anatomy of White and Black people. As Dr. W. T. English[20] wrote:

> A careful inspection reveals the body of the negro a mass of minor defects and imperfections from the crown of the head to the soles of the feet....Cranial structures, wide nasal apertures, receding chins, projecting jaws, all typed the Negro as the lowest species in the Darwinian hierarchy (English cited in Brandt 1978: 21).

These blatantly racist prejudices were replicated in and strengthened by biomedical research. Many researchers have argued that the historical negative experiences of African Americans in clinical research have hampered their participation in the research. Many historical events have hence influenced the contemporary opinions of African Americans towards clinical research. Several studies argue specifically that the tragedy of Tuskegee experiment is mainly responsible for African American distrust of biomedical research (Gamble 1993). By attributing this distrust to a single incidence, these scholars ignore the other historical events which have influenced the attitudes of African American towards clinical research.

Back in the history long before American Civil War, Black people's dead bodies were used for dissections and medical experiments in the US. As documented by the French visitor Harriet Martineau on her trip to the US in 1835, "In Baltimore the

[20] Dr. W. T. English was a physician from Pennsylvania, US.

bodies of coloured people exclusively are taken for dissection, because the Whites do not like it, and the coloured people cannot resist" (Martineu cited in Gamble 1997: 21). During this period, Black slaves in the US were not entitled to civil rights, and the state considered them as property to be exploited by any means. Two experiments were representative of the cruelty of medical experiments on the bodies of black people and the exploitation of Black slaves by White physicians.

First was the experiment carried out by a Georgia physician Thomas Hamilton in order to find out remedies for heatstroke. Thomas Hamilton bought one slave named Fed from his previous master in lieu of the payment of a debt. In order to determine what medication is useful to withstand heat, Hamilton forced Fed to sit naked on a stool placed in a pit which was heated to high temperatures. Fed's head was the only part of his body above ground. Hamilton conducted this experiment for two to three weeks during which period he placed Fed in a pit until the later fainted. After each experiment, Hamilton gave a different medications to Fed to determine which one works better for heatstroke. The whole objective of this experiment was to determine the medication for heatstroke so that Black slaves could administered with the new medicine when they suffered heatstroke (Gamble 1997).

In the second experiment, Dr. J. Marion Sims, who is known to be the father of modern gynaecology, conducted experiments on three slave women to develop an operation technique for repairing Vesico-Vaginal Fistulas (VVF). VVF is a tear in urinary bladder opening into vagina caused by obstructed labour and results in continuous leak of urine through the vagina. Women with this condition were usually outcaste from society, and some even committed suicide because of humiliation. This was also a period when medical examination of the female sexual and reproductive organs was considered as offensive. The male dominated medical profession was influenced by American and European Victorian values and even the diagnosis of diseases related to woman pelvic region was done by looking into eyes of the women. In American medical schools, obstetrics and child delivery was taught by using dummy bodies. Hence automatically White women become untouched by experiments which involved the examination of female reproductive organs. Marion Sims therefore chose to conduct experiments on Black slave women with VVF

disorder. In the antebellum[21] South, slave women were exploited by their masters. They were also victims of malnourishment and lack of prenatal care which placed them at high risk of VVF. Sims enslaved around seven Alabama African Black women and started his experimentation on them in the backyard of his house. All seven slave women slave were brought in by their masters to Dr. Sims because their VVF prevented them from working in the fields. After about thirty unsuccessful operations on these seven slave women, Sims succeeded in developing a technique of repairing VVF. For this achievement, he is referred to as the father of gynaecology. Sims did not ask for these women's consent before the experiments; instead their master's consent was taken. In addition, he invited twelve other doctors to witness his operation, which must have been humiliating for these women. As Dr. Sims elaborated in his biography: "The first patient I operated on was Lucy...That was before the days of anaesthetics, and the poor girl, on her knees, bore the operation with great heroism and bravery" (Sims 1889 cited in Gamble 1997: 1744). The experiment on Lucy was a failure, and according to Dr. Sims, she was about to die during the operation. Despite these failures, he continued his experimentation on the other slave women until he found out a technique to cure VVF. Even though in due course he achieved fame and came to be known as the father of gynaecologist, powerless black women had to endure his unethical experimentation (Ojanuga 1993).

2.2.2 Tuskegee Study

The use of African American black people as study subjects persisted even after the American Civil war. An example of such research is the infamous Tuskegee trial study which led to the deaths of a number of black male participants because they were denied access to medicines. The black people at that time were considered with high libido. According to opinion of medical professionals of that time, Black male have excessive sexual desire and hence they gets attracted to White women easily, which is threatening the purity of the White race. As Dr. English wrote:

> A perversion from which most races are exempt, prompts the negro's inclination towards White women whereas other races incline towards female of their own....gray

[21] Period before that of Civil War

> matter of negro brain to be at least a thousand years behind that of White races, his genital organs were overdeveloped (English 1896 cited in Brandt 1978: 21).

The White medical professionals at that time concluded that a lust for sex; broken families and immorality on part of black people have made them more prone to venereal diseases. According to estimates at that time, 50 per cent of the adult black population was syphilitic (Brandt 1978). Some doctors argued that the high prevalence of the venereal diseases had put black race in danger of extinction. They also attributed the high prevalence of miscarriages and stillbirths to venereal disease. This package of ideas usually formed the perspective concerning black people and their health and illness. It did not take into account the socio economic factors, nutrition, and the exploitation of black people by their masters into account (Brandt 1978). Theses irrational assumptions were reflected in the infamous Tuskegee tragedy as well.

In the Tuskegee study, the United States Public Health Service (USPHS) had initiated an experiment in order to investigate the natural course of untreated syphilis in the year 1932 in Macon County, Alabama. The participants of the study were all black men and the duration of the study was 40 years, the rationale for which was questioned later by an investigatory panel. The study was conducted on a total of 400 syphilitic black men and 200 non-syphilitic people in the control group. During the 1950s, penicillin was widely available for the effective treatment of syphilis. The trial participants were not seen as human. Thus the investigators deliberately denied them access to penicillin. Access to penicillin was denied to all participant syphilis patients, resulting in the death of almost 100 patients directly from advanced syphilitic lesions (Brandt 1978). The Tuskegee study tragedy came into the public domain when research findings were published in the year 1972. There was an uproar, following which the Department of Health, Education and Welfare halted the experiment and appointed an investigatory panel. The report of this panel, which investigated the violation of ethics in the study, came out in the next year. It clearly said that the, study was “ethically unjustified” and questioned the methodology of the study (Brandt 1978). The tragedy came to symbolize of racism in medicine, ethical misconduct in human research, the arrogance of physicians, and government abuse of Black people. The shadow cast by the Tuskegee Syphilis Study on efforts to improve the health status of Black Americans provided an impetus for the campaign for a

presidential apology. Numerous articles, in both the professional and popular press, have pointed out that the study predisposed many African Americans to distrust medical and public health authorities and has led to critically low Black participation in clinical trials and organ donation (Ojanuga 1993). Some researchers like Corbie-Smith et al. interviewed African Americans and tried to investigate latter's attitude to clinical trials participation. They found that interviewees were afraid that White physicians would be dishonest, would treat black people as guinea pigs, and would deliberately not inform them about the risks associated with a study (Corbie-Smith et al. 1999). In a 2002 follow up study, Corbie-Smith et al. found that African Americans were more likely than were Whites to believe that physicians would not fully explain the details of research participation (Corbie-Smith et al. 2002). The study also identified African Americans' stronger fears that their physicians would allow them to participate in a study even if serious harm was anticipated, and one out of four African Americans expressed a high level of distrust in physicians. Likewise, Freedman interviewed African American women in an effort to capture and describe their experiences with research and clinical trials. One woman in the study noted, "We have always had a concern about what White people have done to black people." (Freedman cited in Fisher and Kalbaugh 2011: 2218). The Tuskegee tragedy also had an impact on Human Immunodeficiency Virus (HIV) prevention and treatment programs. One study argues that 'the legacy of this experiment, with its failure to educate the study participants and treat them adequately, laid the foundation for today's pervasive sense of black distrust of public health authorities' (Thomas and Quinn 1991: 1500). The syphilis study has also been used to explain why many African Americans oppose needle exchange programs. Needle exchange programs provoke the image of the syphilis study and Black fears about genocide. These programs are not viewed as mechanisms to stop the spread of HIV but rather as a plot to inject HIV into black people's bodies which has already devastated so much of Black population. The distrust is so pervasive that the state had to step in to win the trust of black people. Thus, on 16th May 1997, twenty five years after the publication of Tuskegee study results, US President Bill Clinton apologized for the injustice faced by African American people during the Tuskegee study. The president said, '*The legacy of the study at Tuskegee has reached far and deep, in ways that hurt our progress and divide our nation. We cannot be one America when*

a whole segment of our nation has no trust in America' (Office of the Press Secretary cited in Gamble 1997: 1773).

2.2.3 GlaxoSmithKline Manipulation of Data

Another example is related to the crucial issue of access to clinical trial data of GlaxoSmithKline's' (GSK) Paroxetine, which is a blockbuster antidepressant approved for marketing for adults. But eventually GSK sponsored *Study 329* with an objective to ascertain the therapeutic value of Paroxetine for children and adolescents. GSK published its results in the *Journal of the American Academy of Child and Adolescent Psychiatry* (JAACAP) claiming its effectiveness in children and adolescents too. But soon the drug ran into a controversy because it increased the suicidal tendencies among children and adolescents. In 2003, the Committee on Safety of Medicines banned the use of the medicine in the United Kingdom (UK), citing increased risk of self harm and potential suicidal behaviour among children. In the US also, the United States Food and Drug Administration (USFDA) placed a boxed warning stating the side effects of medicines in children. Long time before that, Jon Jureidini, a clinical professor of psychiatry at the University of Adelaide, was pleading a case against GSK asking to reanalyze and republish the results of *Study 329* (Doshi 2013). Following the lawsuit, in 2012, GSK was asked to pay three billion dollars because the Department of Justice found in its investigation that the article published in JAACAP had distorted the study results. In spite of getting negative results, the study had manipulated data and published it as a positive result (Doshi 2013). This case provoked debates regarding access of clinical trial data to the public. Following this embarrassment, GSK agreed to register all their trials with detail methods, along with results. However companies such as InterMune and Abbvie, on the other hand, filed lawsuit demanding that the court should not allow access to clinical trial related data (Doshi 2013). According to the Food and Drug Administration Amendments Act (FDAAA), 2007, it is mandatory to publish results of some trials on the US federal registry, Clinicaltrials.gov. These trials include non-phase I trials, investigational drugs and medical devices with at least one clinical trial site from US. But the study conducted by Anderson et al., found that out of around 13,000 trials registered in the registry, only 13.4 per cent trials had published their

results (Wallan 2015). When trials are exclusively from non-US sites, the publication rate is worse. In 2007, according to FDAAA, around 53 per cent of trials were being conducted outside of the US and it was not mandatory to publish their results. Since there is no requirement for the publication of results for a large numbers of trials, it is very difficult to find the number of deaths and other SAEs occurring during these trials.

2.2.4 Current Trends of Expropriation in the US

Historical injustice to African American people has resulted in minimal participation of these communities in clinical research. Reports related to clinical trials have revealed that only 12.4 per cent and 15.8 per cent of total participants are of African American and Hispanic communities respectively (Fisher and Kalbaugh 2011). A recent report indicates that minorities[22] represent almost 30 per cent of those enrolled in clinical trials sponsored by the National Institutes of Health (NIH), and that African Americans now constitute about 15 per cent of the minority participants. However significant enrolment issues have continuing to affect the representation of Hispanics in clinical trials. One report estimated Hispanic representation in NIH studies at 7.6 per cent of all research participants and a report on industry sponsored studies found that only three per cent of those participants were Hispanic (Pinn et al. 2009 cited in Fisher and Kalbaugh 2011). During the last 25 years, there has been nationwide effort to enhance the participation of these communities in clinical research. One milestone in the US regulations of clinical trials is the Belmont Report (1979). Written by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, this report was an effort to highlight the principles needed to guide the ethical conduct of human participant research and to protect them against tragedies like the Tuskegee Syphilis Study. One of the ethical principles outlined in the Belmont Report is that of justice, which is related with the fair distribution of the benefits and burdens of medical research on the population. Yet, even with the protections of research participants envisioned in the years after the publication of the Belmont Report, minority participation in clinical research has remained low. These low enrolment numbers resulted in the enactment of new

[22] Minorities community here constitutes African American black and Hispanics

legislation, such as the NIHR[23] Vitalization Act of 1993, which has a section titled *Inclusion of Women and Minorities* specifically addressing issues of women and African American people and to enhance their participation in clinical trials research (Fisher and Kalbaugh 2011). The US President's apology for Tuskegee tragedy can also be analyzed in the same light as part of government's efforts to increase the participation of minorities in clinical research.

According to the arguments of scientific community, increasing the participation of minorities in clinical trials is necessary for the production of knowledge about new therapies because having diverse research participants can improve the generalizability of medicine. The basic argument made by the researchers is that due to their lack of participation, minorities are not getting access to improved therapies which they might get through participation in the clinical trial. But there is a hardly any discussion on the issue of higher participation of minorities in the high risk and zero benefit phase I trials. Apart from this, all mainstream research fails to analyze the participation of minorities across the different phases of clinical trials. Much of the literature instead focuses on analysis of phase III therapeutic trials and fails to address the issues of minorities' participation in initial phases of trials. When Fisher and Kalbaugh analyzed the participation of minorities across trials and region, they found the minority population is overrepresented in phase I trials (See Table 2.1). Phase I trials are non therapeutic and hence minorities end up getting some financial compensation along with the short term or long term side effects on their bodies (Fisher and Kalbaugh 2011).

[23] National Institute for Health Research

Table 2.1

Demographics of Phase I Participants at One Northeastern and one Southwestern US Facility

Demographic Factor	Phase I Facilities		
	Northeast	**Southwest**	**Total**
Total Participants	13612	16747	30359
Gender, no. (%)			
Men	9241 (67.9)	9306 (55.6)	18547 (61.1)
Women	4371 (32.1)	7441 (44.4)	11812 (38.9)
White, non-Hispanic, no. (%)	4735 (34.8)	6230 (37.2)	10965 (36.1)
All non-White, no. (%)	8877 (65.2)	10517 (62.8)	19394 (63.9)
African American	5755 (42.3)	1027 (6.1)	6782 (22.3)
Asian	423 (3.1)	99 (0.6)	522 (1.7)
Hispanic	1970 (14.5)	9196 (54.9)	11166 (36.8)
Other	729 (5.4)	195 (1.2)	924 (3.0)

Source: *Challenging Assumptions about Minority Participation in US Clinical Research* (Fisher and Kalbaugh 2011: 2218)

Note: The data are from 2 companies' ''active'' participant databases as queried in June 2010. The companies' identities are confidential as part of their participation in a broader, ongoing empirical project. Fisher and Kalbaugh selected them on the basis of their large participant data bases and the high volume of studies they conduct for industry, which makes them representative of phase I trials conducted in the United States. Facilities with smaller data bases of participants report similar demographic data.

As part of a larger empirical project on phase I clinical trials in the United States, Fisher and Kalbaugh obtained demographic data on healthy volunteers from two of the largest phase I facilities in the country: one in the Northeast and one in the Southwest US. In both facilities, the percentage of minority participants is much greater than that of White volunteers (63.9 per cent compared with 36.1 per cent, respectively). African Americans make up 42.3 per cent of the healthy volunteers in the Northeast and 6.1 per cent in the Southwest, with an average of 22.3 per cent between the two facilities. This figure represents nearly double the proportion of African Americans one would expect on the basis of population alone. Hispanics

make up 14.5 per cent of the healthy volunteers in the Northeast and 54.9 per cent in the Southwest, with an average of 36.8 per cent between the two facilities. These findings reveals that Hispanics are represented at more than twice the rate expected on the basis of US population statistics and almost five times their representation in NIH sponsored phase III studies. Though this data is not definitive, but it illustrates that minority participation in phase I trials is higher than expected on the basis of US demographic data and their representation in therapeutic trials (Fisher and Kalbaugh 2011).

2.3 Clinical Trial Tragedies in India

In India, there is no study which has analyzed the socio-economic backgrounds of clinical trial participants. In fact, there is no provision in the consent form which can note down the socioeconomic background of the clinical trial participants[24]. But there are a number of case studies which reveal that the victims of clinical trials are mostly from lower socioeconomic backgrounds. Caste, class and gender play a major role in the victimization of the marginalized population in the clinical trial industry. The terrain of clinical trials is very complex in the Indian context and a number of factors such as the unavailability of public health services, the unaffordability of private health services and the doctor-patient power relations influence people decision making related participation in trials. Public health services are already at its worst, with state spending only about one per cent of Gross Domestic Product (GDP) on health (Kalra 2015). Since independence, the government has continuously slashed the funds allocated to public health services. Out of Rs. 1500 billion spend on social sector, Indian government is spending only 15 per cent on health sector. With miniscule contribution from social and private health insurance, around 80 per cent is spent from individual pockets out of which 70 per cent are the poor (Duggal 2005). India accounts for the highest number of maternal deaths in the world. India and Nigeria (14 per cent), account for the one-third of the global maternal deaths. The National Rural Health Mission (NRHM) aimed to reduce the Infant Mortality Rate (IMR) to 28 per 1000 live births, the Maternal Mortality Ratio (MMR) to 100 per 100000 live births by 2012. With the IMR at 44 and the MMR at 190 in 2012, India

[24] This observation is based on analysis of copy of consent form recovered during field work

lags behind the other developing countries on these indicators (Kurian 2015). The difference is stark even when we analyze the indicators for the rich and poor. The poor-rich risk ratio is 2.5 for infant mortality, 2.8 for under–five mortality and 1.7 for childhood underweight (Peters 2002). India's health indicators are one of the worst in the world. The health indicators of India suggest that inequalities across classes are very wide. For example, the infant and child mortality rates are 2.5 times lower in the top 18 per cent than the bottom 36 per cent households (Gangolli et al. 2005). This is clearly due to inadequate access to healthcare services, because even in conditions of poverty, if access to primary healthcare is universal then poor can access these services. When it comes to hospitalised treatment, the richest quintile of the population, despite overall better health status, is six times more likely to access hospitalisation than the poorest quintile of the population (Gangolli et al. 2005). This means that the poor are unable to afford and access hospitalisation in a large proportion of illness episodes, even when it is required

The ineffectiveness of the Indian health system and the characteristically high health-related out-of-pocket hospital payments push around 60 million people- roughly UK's population below poverty line every year. The out-of-pocket expenditure is one of the major causes of indebtedness in India. The cost of the medicine is one of the largest factors that contribute to the out-of-pocket expenditure. Medicines account for 70 per cent of the out-of-pocket expenditure (Garg and Karan 2009). The poor patients, for whom the private health services are unaffordable, usually try to avail public health services. Even though she or he is getting free check up at the public health facilities, the patients are forced to buy medicines from private chemist because medicines are usually out of stock in the government pharmacies. Many government doctors have also questioned the quality of the generic medicines and hence refuse to prescribe it. Those who are availing the private health services are also exploited through prescribing branded medicines. The nexus between pharmaceutical companies and doctors' mediated by medical representative has been exposed by a number of studies (Bansal and Das 2005). The cost of medicines bought from the private medical stores can be two to forty times more than that of the generic medicines available at the public facilities (Medicine Pricing and Universal Access to Treatment n.d.). Hence the universal access to medicine has become a crucial issue in India and requires urgent attention.

In 2005, the Indian government took several measures to promote clinical trial sector in the country. It was also a year when India gave up its product patent regime. Changes were made in the rules and regulations to facilitate Global Clinical Trials (GCT) in India. The development of human resource, infrastructure improvements, the establishment of monitoring systems and training institutes were some of the measures taken by the Indian government to drug regulatory authorities like USFDA. Medical researchers were offered substantial incentives to become principle investigators and conduct trials on their patients (Singh 2008). The Contract Research Organizations (CROs) in collusion with doctors tried to exploit this context by luring people who do not have access to private health care services and the public health services fail to meet their health needs. With the promises as 'the medicine is from foreign company and at free of cost' patients were lured to participate in trials (State Economic Offences Investigation Bureau Madhya Pradesh 2011).

A CRO called Excel Life Sciences conducted a survey in July 2008 and interviewed 525 patients from 40 sites. The findings of this survey suggest that the, 76 per cent of patients said the trial's principal investigator was their primary physician. A further 21 per cent said they were referred by their primary care physician to participate in the trial. That means around 97 per cent of patients entered the trial because of influence of their primary care physician (Srinivasan and Nikarge 2009). It is a well known fact that the doctor-patient relationship in India is unequal. Patients in India trust their doctors because of information asymmetry. They do not question their doctor's diagnosis and prescribed course of treatment and get easily influenced by his or her advice. Invisible structural power asymmetry also exists in the patient-doctor relationship. Patients believe that a refusal to follow the doctor's advice to participate in a trial would affect their access to care.

Another section of the Excel Life Sciences survey on 'why do people participate in trials' reports that: 26 per cent of participants stated that they entered the trial to obtain free care or higher quality care while five percent people participated in the trial because of financial incentives (Srinivasan and Nikarge 2009). On the one hand, the Indian Council of Medical Research (ICMR) ethical guidelines for biomedical research on human participants states that, "payments should not be so large or the medical services so extensive as to make prospective participants consent readily to

enrol in research against their better judgment, which would then be treated as undue inducement" (Indian Council of Medical Research 2006: 25). On the other hand, it remains silent on the financial incentives to doctors and CROs. It is true that the research is ethical when participants are motivated by altruistic motive, but the ICMR guideline perpetrate injustice to research participants by regulating their behaviour while remaining silent on the financial benefits to other stakeholders. In addition, when any incidence of SAE or death occurs, patients are denied access to treatment and compensation. Let us look at then some of the clinical trial tragedies from India.

2.3.1 1990s ICMR[25] Study on Women

In 1986, Stree Shakti Sanghatan, Saheli, Chingari and several other activists filed a writ petition in the Supreme Court of India asking for a ban on the phase IV clinical trial of Norethisterone Enathane (Net En), an injectable contraceptive. During the trial, not only was the process of informed consent compromised, the hazards of the drug were also not shared with participants. In response to the petition, the government recognized the potential risks of injectable contraceptives and admitted that unless there is well equipped health service system, mass use of Net En is a risky affair. The sad part of the story was that the trial was conducted in a family planning camp in the Patancheru primary health centre and women did not know that they were administered an unapproved contraceptive or that they were participating in its trial. Although Net En has short term side effects like irregular menstrual cycle and adverse impact on the hypothalamus-pituitary axis in the brain, these severe side effects were not shared with women. Its long term side effects include risk of cancer and risk to progeny. These called for close monitoring and follow up by health services, both of which were not in place (Bal et al. 2010).

[25] Indian Council of Medical Research

2.3.2 Human Papilloma Virus Vaccine Tragedy

History was repeated when the Andhra Pradesh Ministry for Health and Family Welfare in association with ICMR and PATH International launched what it described as a *demonstration project* for vaccination against cervical cancer. The vaccine against the Human Papillomavirus (HPV) was administered to 14,000 girls between the ages of 10 to 14 in Khammam district of Andhra Pradesh. In Andhra Pradesh, the administered vaccine was Gardasil, manufactured by Merck Sharpe and Dohme, the Indian subsidiary of Merck and Co. Inc., a US-based pharmaceutical company. In a similar kind of project the Gujarat government launched a two year *Demonstration Project for Cancer of the Cervix Vaccine* in three blocks of Vadodara District to administer three doses of the HPV vaccine to 16,000 girls between 10 and 14 years. The Gujarat State Minister for Health and Family Welfare claimed that this *demonstration project* would help the Central Government assess the possibility of including the vaccine in the Universal Immunization Programme.

When the incidences of deaths were reported in the media, the fact finding team of several women right activists visited the trial site in Andhra Pradesh. According to their findings, the children who were part of this project were mainly from the four social groups: scheduled tribes, scheduled castes, Muslims and the other backward communities. The majority of children vaccinated were tribals and with parents who were mostly agricultural labourers. Few girls were from families that have been displaced by the ongoing Maoist-state conflict in the neighbouring state of Chhattisgarh. Malnutrition, malaria, dengue, diarrhoea, chikungunya and other health problems are rampant in this area, which is also marked by the absence of accessible public health facilities. Children were suffering from a range of health problems due to poverty, lack of access to nutrition and the absence of health services (Sarojini et al. 2010).

There were serious violations of research ethics during the trial. In some cases, the teachers in charge or hostel wardens gave their consent on behalf of girls to participate in the study. The process of consent taking was a mere formality because many girls did not understand what cervical cancer is, and nor were their parents informed about it. The HPV immunization cards given to parents were in English and misleading. The HPV immunization cards as well as the banners had the NRHM

and PATH logos, while the consent form has the contact addresses of the District Immunization Officer and a PATH official. As the logo of the National Rural Health Mission (NRHM) was used, many parents thought the trial to be a government run vaccination programme. There were reports of the deaths of four girls following the administration of one to three doses of the vaccine. There were also other SAEs such as mood swings, irritability and agitation, seizures and a general feeling of uneasiness, reported by girls in Bhadrachalam. Other reported side effects have included severe headaches and stomach aches, dizziness, an early onset of menstruation soon after the vaccination and heavy bleeding. These side effects were overlooked by PATH and the study was continued. At the end, different women groups filed a writ petition in the Supreme Court seeking a stay on the study. The Supreme Court took cognizance of the issues and immediately stayed the study (Sarojini et al. 2010).

2.3.3 Campaign against Unethical and Illegal Clinical Trials in India

This campaign initiated when a series of irregularities surfaced in a state of Madhya Pradesh, India. In 2010, irregularities in clinical trials conducted in Mahatma Gandhi Memorial (MGM) Medical College, Indore became headlines. Following this, several health rights activists filed a number of applications under the Right to Information (RTI) Act, 2005 seeking information related to clinical trials in Madhya Pradesh. The complaint was registered with the State Economic Offences Wing (EOW) against five doctors from MGM medical college who allegedly received money from the multinational pharmaceuticals. The said trials had been conducted in the government hospital using government resources on patients who had visited the government hospitals for a treatment. But the individual doctors received money in their personal accounts and did not pay the institutional share. On the grounds of confidentiality, State Public Information office denied sharing the details of patients on whom trials had been conducted, number and nature of SAEs. The issue was raised in the legislative assembly of Madhya Pradesh by an independent Member of Legislative Assembly (MLA) Paras Saklecha. The health right activists also got the valuable information regarding the illegal clinical trials through answers to questions

raised by MLAs. Then after series of deaths and other SAEs related to clinical trials surfaced out in local media (Swasthya Adhikar Manch 2010).

In 2011, the first case of Sheela Gite came into the limelight. in the year 2011. Late Sheela Gite who lived in Khandwa, Madhya Pradesh was suffering from Alzheimer's. She was admitted in the Neurological department of Maharaja Yeshwantroa Hospital (MYH), Indore, in 2008. After the diagnosis, Dr Apoorva Puranik, the chief medical officer told her husband, Sharad Gite that currently an Alzheimer's disease study was going on in the hospital and all medicines related to this disease have come from the foreign multinational companies. He also told that medicines were very effective and the treatment would be free of cost and that the travelling allowance would be paid from Khandwa to Indore. He also assured that the study was completely safe and any injury occurring during the study was covered under the insurance. Accepting the doctor's advice, Sharad Gite signed the consent form and enrolled her wife in the study. After that Sheela Gite's treatment was started under Dr Apoorva Pooranik and she was administered medicines without any name written on their wrappers. Soon the health condition of Sheela started deteriorating and when her husband asked doctors about the therapeutic potential of the administered medicines, he was assured that wife would be cured. On 8th August 2010, Sheela Gite died and the insurance amount was never paid to her husband. (Swasthya Adhikar Manch 2012).

In another case of Srikrishna Gehlod who was a resident of Banganj area in Indore, there were serious violations of ethics. Srikrishna Gehlod was a tailor by profession and was working on daily wage basis in a shop. Through minuscule income he had earned through tailoring, he bought an auto rickshaw for his son who is now working as an auto rickshaw driver. In January 2009, Srikrishna Gehalod was admitted in Manorama Raje TB Hospital and Chest Centre, Indore associated with Mahatma Gandhi Memorial (MGM) Medical College, under the observation of Dr. Ashok Bajpai. His diagnosis revealed that he was suffering from Chronic Obstructive Pulmonary Disease (COPD). While taking treatment, he was informed by Dr. Saurabh Jain an assistant doctor of Dr Bajpai that an American company is providing free medicine for his treatment which better than the medicines provided by the

hospital. Doctors convinced him for this American medicine and probably took his signature. Dr. Bajpai conducted a trial titled 'Study to assess the safety and efficacy of 48 weeks of once daily treatment of orally inhaled B1 1744 CL 5µg and 10 µg respiratory inhaler and Foradil delivered by aerolizer inhaler in patient with COPD' on him. This trial was supported by Boehringer Ingelheim Phrmaceuticals, a Germany based company. During the duration of one year of the study, he was once offered 300 rupees for transportation. He used to walk and do other things before the trial but at the end of it he was bedridden and lost his job. When the health activists from Swasthya Adhikar Manch visited his house, he finally came to know that a new drug was tried on him. Following that he filed a complaint in National Human Rights Commission that without his consent, trial was conducted on him which resulted in physical deterioration in his health. After few months, Srikrishna Gehlod died and his son is still fighting for the compensation and justice (Swasthya Adhikar Manch 2012).

Following many of such cases in the media put pressure on State government to table the EOW investigation report in the legislative assembly for the discussion. In the EOW Madhya Pradesh investigation report it has been reported that in the 73 protocols relating to which trials were carried out, 81 persons suffered serious side effects even leading to death, which included 18 children. These issues were not disclosed by the Ethics Committee nor were any compensation paid to the victims.

The report found following irregularities and shortcomings during investigation (State Economic Offences Investigation Bureau Madhya Pradesh 2011).

1. The Principal Investigators (PIs) were themselves the members or member secretaries in the Ethical Committees and these committees did not follow the standard practices and ethical guidelines fully.
2. The Principal Investigator and the Ethical Committee did not take appropriate steps as was expected from them in cases of Serious Adverse Events (SAEs).
3. CROs, Ethical Committee and PIs did not follow the established principles of safeguarding the interest of the patients.
4. The core principles of informed consent were disregarded.
5. On several Instances the Principal Investigator contravened the Section 20 A (Professional Conduct) of the Indian Medical Council Act, 1956.

6. By accepting money for themselves and by undertaking sponsored foreign trips the Principal Investigator clearly contravened the *conflict of interest* doctrine.
7. The trials did not in any way follow the established rules which would have ensured profits to the institutions where they were carried out. The institutions did not gain in particular from the trials carried out by the PIs.
8. The patients on whom the drug trials were carried out deposed that no transparency was displayed while carrying out trials and they were even denied entitlements that were due to them.
9. In instances of Serious Adverse Effects the dictum of financial safeguard or insurance was contravened.

Based on these shortcomings report further recommended some action as given below:

1. For not safeguarding the interest of the patients as per the established principles by the CROs, Ethical Committees and PIs, for not conforming to the laid out guidelines by the institutions where the trials were carried out, for contravening the financial safeguards/insurance dictates actions should be taken as per law by the State Medical Council against the Principal Investigators and members of the Ethical Committees.
2. For disregarding the core principles of informed consent, for not maintaining transparency and for denying the trial subjects of their due entitlements, and for violating the principals of *Ethical Guidelines for Biomedical Research on Human Participants*, ICMR should contemplate taking appropriate action against the Principal Investigators, Ethical Committees and CROs.
3. Action could be contemplated under the conduct rules of State Medical Education department of Government of Madhya Pradesh as the trials did not in any way follow the established rules which would have ensured profits to the institutions where they were carried out. The institutions did not gain in particular from the trials carried out by the PIs.
4. The government should consider taking action by following up with the Medical Council of India (MCI) against the PIs for accepting money for themselves and by undertaking sponsored foreign trips under code of medical ethics regulation 2002 and amendment notification dated 10 December, 2009 of MCI.

5. Out of the money received from clinical trials 10 per cent was to be deposited in the Medical Education Department account of MGM Medical College, Indore, which still under consideration and which has still not been deposited.

Other long term recommendations of the Bureau were:

1. There should be clear guidelines for composition, constitution and responsibilities of the Ethics Committee and the members of the Ethics Committee should not be permitted to conduct trials, so that the entire process is conducted in impartial and transparent manner. If any doctor wants to do drug trial then it is not appropriate to keep him/her in the Ethics Committee, rather even after one year of completion of drug trial he/she should not become part of the ethics committee.
2. There is a need on part of government to prepare clear rules and guidelines relating to money received on account of drug trials done. There is a need to make rules with respect to the manner in which record of all receipts would be made, the ratio of distribution to be made between doctors and drug trial staff.
3. While filing application before the Ethics Committee it should be disclosed in the first instance regarding the doctor or paramedic staff who would be undertaking foreign trips and the ethics committee should examine the purpose of these trips.
4. If during the trial there is a serious adverse effect or death then the entire responsibility of ensuring that the deceased family gets insurance compensation should lie on the doctor and the sponsor company so that the claimant's rights are settled in time.
5. Before starting the drug trial, written prior consent of the subject should be obtained and the patient should be given complete information in relation to drug trial. There is a need for making comprehensive guidelines on this issue also. While the patients are being educated about drug trial witness should be present and videography should be done and placed on record.
6. A law should be made to ensure that if the patient died then a post-mortem/autopsy should be done.

But different state ministers came in to support of the doctors and claimed that there is no any such irregularity and hence action cannot be taken. Hence Swasthya

Adhikar Manch, an umbrella organization of various groups working in the field of health in Madhya Pradesh filed a Public Interest Litigation (PIL) in the Supreme Court in February 2012. The petition sought regulation of clinical trials in the India and justice for the victims of unethical and illegal clinical trials. This is the first time that the issue of unethical clinical trials was raised in the Supreme Court of India by way of Public Interest Litigation. Since then there are number of hearing in the Supreme Court and court has taken the cognizance of the facts presented by the Swasthya Adhikar Manch. After information related to deaths and SAEs during clinical trial since year 2005 was revealed in the Supreme Court, the gravity of the problem was realized (See Table 2.2). In July 2012 following Supreme Court order, the DCGI constituted two committees called apex committee and technical committee to screen the clinical trial proposals. Three parameters for the screening have also been laid down by Supreme Court and they are *risk versus benefits, innovations versus existing therapy and unmet need to the Indian population*. The data related socio-economic background of the clinical trial participants who have suffered either death or SAEs has not been submitted even after consistent demand in the Supreme Court. In fact CROs and hospitals have not maintained this data at all. Even the consent form does not have any kind of column which will stress the socio-economic background of the clinical trial participants.

Table 2.2

Number of SAEs and Deaths 'due to' and 'during' Clinical Trials for the Period of January 2005 to December 2013

Sr. No.	Type	Jan 05 to June 12	July 12 to Dec 12	Jan 13 to Dec 13	Total
1	SAEs	11972	1226	1122	14320
2	Deaths	2644	224	590	3458
3	**Total**	**14616**	**1450**	**2938**	**17778**
4	SAEs due to trials	506	INP	INP	506
5	Deaths due to trials	80	9	INP	89
6	Compensated only in deaths not in SAEs	80	9	INP	89

Source: Swasthya Adhikar Manch v Union of India and others, No. 33 of 2012 (2012: 32)

Note: INP-Information Not Provided

The Ministry of Health and Family Welfare (MoHFW) still has not given complete information about 17,778 (3458 deaths and 14,320 SAEs) which has taken place from January 2005 to December 2013 except stating that in 89 cases compensation has been paid. The Ministry has not disclosed the names of persons who have died and to whom compensation has been paid. The Ministry has also not given any detail of payment of compensation paid to the SAEs. The MoHFW has also said in the court that that there were no rules regarding compensation, therefore compensation cannot be paid. MoHFW also do not have any records of 475 clinical trials of New Chemical Entities (NCEs). This fact speaks volumes about causal and negligent manner in which ministry was acting. Further it also shows that Drug Controller General of India (DCGI) was functioning in collusion with drug industries. It can be also said that three parameters namely, risk versus benefits, innovations versus existing therapy and unmet need to the Indian population have not been followed in letter and spirit both by technical committee and apex committee. In a routine way

the technical committee had approved 76 clinical trials out of 78 NCEs plus 43 fresh proposals, a total 119 trials in its sixteenth meeting on 10th July 2014 within few hours. It is incomprehensible that the detailed parameters of 78 NCEs could have been analyzed scientifically in one day (Swasthya Adhikar Manch 2012). The vested interests of the members of committees are also visible. For Example, the Chairman of the Apex Committee for the approval of the clinical trial proposal is Dr. Ranjit Roy Chaudhury. He is presently also the Chairman of the Task Force for Research of Apollo Hospitals Educational and Research Foundation one of the biggest private health care provider and clinical research institute in India (LifeScienceWorld 2012). So there is a possibility of the vested interests in the approval given by Apex Committee.

2.3.4 Clinical Trials on Victims of Bhopal Gas Tragedy

In the early morning hours of December 3, 1984, the gravest industrial disaster happened in Bhopal, Madhya Pradesh, India when poisonous gas leaked from the Union Carbide Plant and rolled over the city. Around forty tons of toxic gas Methyl-Iso-Cyanate (MIC) was released from Union Carbide's Bhopal plant, which leaked and spread throughout the city. The effect was so much devastating that people awoke suffocating short of breath and started running frightened through the dark streets. Many of the victims who arrived at nearby hospitals were breathless and blind. Not only lungs or eyes but brain, muscles as well as gastro-intestinal, neurological, reproductive and immune systems of those who survived were severely affected. The poor slum dwellers and pavement dwellers those who do not have proper housing were mostly affected because of this disaster. On the next day, actually the gravity of the disaster was realized when dead bodies of people were piled up on the streets. An estimated 10,000 or more people died. About 500,000 more people suffered permanent injuries with disastrous effects of the massive poisoning and it is still continued to next generations (Pandeya 2010).

The victim's organization called Bhopal Gas Peedith Sangharsh Sahayog Samiti (BGPSSS) was formed by the Bhopal gas victims in 1986 in their quest for justice. In response to this tragedy and injustice on part of Union Carbide and government the BGPSSS filed a writ petition in the Supreme Court for the demand of punishing the culprit and rehabilitation of victims. Around thirty years after the disaster, the

victims of the Bhopal gas tragedy are struggling for the justice. Supreme Court has already taken the cognizance of the issue and had directed the Government of Madhya Pradesh to provide free food rations and 750 rupees per month to the gas-exposed families of gas tragedy victims. Supreme Court had also directed the central government to establish one hospital to deliver the health services to the victims and their family members. Hence Bhopal Memorial Hospital and Research Centre was established under ICMR.

The clinical trials that were carried out in the Bhopal Memorial Hospital and Research Centre (BMHRC) on the gas-victims were exposed in January, 2010 when the Convener of Bhopal Gas Peedith Mahila Udyog Sanghatan (BGPMUS), Mr. Abdul Jabbar Khan, accidently came across a circular from the Director, BMHRC, directing the Departmental Heads of Cardiology, G.I. Surgery, Anesthesia, and Pulmonary Medicine 'to suspend all the ongoing and proposed Drug Trials in your Department with immediate effect'. The said circular was apparently issued following a telephonic communication that the Director, BMHRC, had received from the Secretary of the Bhopal Memorial Hospital Trust (BMHT) on the same day. The BGPMUS then filed a RTI application to obtain necessary information from BMHRC regarding the said clinical trials. The BMHRC was not in a mind to share the information related clinical trials conducted on Bhopal gas victims and hence in reply said that BMHRC does not fall under the purview of RTI Act, 2005 (Bhopal Gas Peedith Mahila and Udyog Sanghatan 2012).

Subsequently substantial information regarding the clinical trials that were conducted at BMHRC during year 2004 to 2008 came into the public domain. From such available information, it appeared that at least 215 gas victims at BMHRC had been subjected to clinical trials. These clinical trials were apparently conducted at the behest of several multinational pharmaceutical companies. As it has appeared in the print and electronic media, the pharmaceutical companies were Theravance Inc., Wyeth Research (now part of Pfizer), Sanofi-Synthelabo (now Sanofi-Aventis), AstraZeneca, Schering, GlaxoSmithKline, etc. From these trials BMHRC allegedly earned over Rs. 100 lakhs for facilitating the process. The gas-victims on whom such trials were conducted were not compensated with a single penny. According to information shared by victims, the name of the drug which was administered was written in code words. Hence it can be said that clinical trial of NCEs which has not

been approved for marketing was conducted on the victims. In majority of the cases, the patients' prior informed consent was not taken. From some patients signatures were taken on the consent form which was in English. In short, the Bhopal gas-victims who were already undergoing suffering on account of exposure to MIC were subjected to clinical trials for a new chemical entity. The adverse impact and deaths which occurred because of the said clinical trials has not been made public; even families of patients were not informed about trials or about those who suffered adverse impact or died. According to a report of inspection, a Central Drug Standard Control Organization (CDSCO) team, which inspected BMHRC in August 2010 on the directive of the Drug Controller General of India (DCGI), has reported severe irregularities on part of the BMHRC doctors. The CDSCO has apparently reported that the hospital authorities not only hid the facts but also submitted false statements to the inspecting team. The BMHRC also failed to maintain trial records in accordance with established rules. Report also shows that BMHRC did not have an accredited institutional ethics committee and the one it had was recruited by the hospital management and was working without a standard operating procedure and with little insight into how patients should be protected. Several gas-victims have also reportedly died during or soon after those drug trials, which too is a matter of grave concern (Pandeya 2010).

It is a dual exploitation of unethical manner in which Bhopal gas-victims were used as guinea pigs in several clinical trials. It is irony on part of ICMR that it had shown inability and hence abandoned the research related Bhopal disaster way back in 1994 and had not bothered to properly study and document the long term impact of MIC on gas-victims, the gas-victims were being made subjects of studies to test the efficacy of various drugs. Under such circumstances, to have treated gas-victims as guinea pigs was morally and ethically unacceptable. The very scientific value of testing drugs on gas victims when the long-term effects of exposure to MIC are poorly understood is also highly questionable (Bhopal Gas Peedith Mahila and Udyog Sanghatan 2012).

2.3.5 Death of 254 Women in Cervical Cancer Screening Clinical Trials

In spite of numbers of struggles against unethical and illegal clinical trial tragedies, the death count is still continuing. There was a recent row over death of 254 women during cervical cancer screening clinical trials funded by US in a year 2014. The trial was aimed at to determine cheap screening treatment for cervical cancer in a sample from three clusters of India. The study compared the cervical cancer deaths among 224,929 women who had been offered different types of cervical screening against 138,624 women to whom no screening was offered. The trial was conducted selectively on women from lower socioeconomic background from slums in Mumbai, villages in Osmanabad district of Maharashtra and Dindigul district in Tamil Nadu. It is well known fact in the medical community that cervical screening reduces the incidence of the cancer but still more than lakh women kept away from screening just because of study objective demands. After the issue was being surfaced in news, the United States Office for Human Research Protections (OHRP) did a detailed investigation and found that women were not informed about the study (United States Office for Human Research Protections 2014). The study violated both international and national ethical guidelines which says that 'the benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention' in a Helsinki Declarations. The study also flouted ICMR guidelines which clearly states that a placebo can only be used only when there is no existing method of treatment. The women were least informed otherwise they would have withdrawn themselves from the study and seek for their choice of screening (Srinivasan 2013).

2.4 Summary

US have a long history of the exploitation of the African American population through institution of slavery. It replicates in the medical research as well where African Americans were always treated as experimental bodies throughout the history. Following the several clinical trial tragedies like Tuskegee, the overall participation of the African Americans decreased in the clinical research. But details investigation of the data available reveals that, African American and Hispanic

communities are still vulnerable and their participation in risky phase I trials is very high as compare to White population.

In Indian context, caste, class and gender plays a major factor while recruiting the clinical trial volunteers. In India, the power dynamics between doctor and patients, information asymmetry plays an important role. As public health services are inadequate and private health services are unaffordable, the patients are usually lured by the doctors saying the medicine is imported and effective, treatment will be free. Either it may be a HPV vaccine tragedy, or unethical and illegal practices in Madhya Pradesh or trials on victims of Bhopal Gas tragedy, the marginalized and poor were the always target of the clinical trials. Recent data revealed in the Supreme Courts tells that, there are around 17748 SAEs during the trials out of which 3458 are deaths but only in 89 cases, the compensation was paid.

Chapter 3

Pharmaceutical Innovation based Economy and Commercialization of Life of Healthy Volunteers

3.1 Expropriation in Marxian View

Karl Marx distinguishes two types of private property and they are scattered private property arising from individual labour and capitalist private property. He explains the transition of former kind of property to later type by elaborating socio-economic processes in late medieval England. During the late medieval period, serfdom disappeared and the main population of free peasant proprietors i.e. *yeomen* was created. The feudal system was replaced by independent farmers. There were two causes behind the dissolution of feudal system: one was pressure of a *Crown* which wanted to establish its absolute power. Hence people were given individual property rights of their land but with the interest of capital industry. The second cause was expansion of Flemish wool manufacturing which required more land under pasteurization (Marx 1981). So it resulted in acquiring common land for pasteurization hence restricting the access of people to common land. This resulted in legalizing the act of usurpation where state could charge taxes from people and at same times could acquire land for capital interest. Marx says, 'the law itself now becomes the instrument by which the people's land is stolen' (Marx 1981: 888). In the second phase of Industrial Revolution, the demand for land increased and the distribution of the state land to industries occurred. In the final stage of the *clearing* of the estates, the aggressive clearing of cottages were done so that the peasants could neither find land for tilling nor a small space for their own house. Marx summarizes the expropriation as:

> The spoliation of the Church's property, the fraudulent alienation of the state domains, the theft of the common lands, the usurpation of feudal and clan property, and its transformation into modern, private property under circumstances of ruthless terrorism, all these things were just so may idyllic methods of primitive accumulation. They conquered the field for capitalist agriculture, incorporated the soil into capital, and created for the urban industries the necessary supplies of free and rightless proletarian (Marx 1981: 888).

This process of land grabbing is also called as *Enclosure* which has a history since 12th century England but reaches its peak in a period from 1750 to 1860 after the enactment of the Enclosure Act. This was also a period of Industrial Revolution in England. Therefore it is necessary to analyze the Enclosure movement in a context of Industrial Revolution. Critic of the Enclosure Act alleged that the act resulted in driving landless poor to the cities so that it can feed to industrial cheap labour demand (McElroy 2012). The migration of the worker was not due to new opportunities posed by Industrial Revolution but more deplorable conditions created due to Enclosure movement forced them to migrate to the cities in search of livelihood.

The actual meaning of the Enclosure is consolidation of land in another way it can be called as a commercialization of the agricultural land so that productivity of the vast consolidated land can be increased through mechanization, rotation of crops and plantation of cash crops. The *British General Enclosure Act, 1801,* removed the prior individual rights of local village population on the land they were tilling since number of generations. According to this act, when the round of enclosure began by petition in the parliament, the politically dominant landowner class turned everything on their side. The commissioners who were allotting the enclosed land were of the same class and hence they allotted best fertile land with plenty of water and wood to big landowners. The acquired land was then transferred to the politically connected landlords who converted them in big farms and invest their capital in land to produce crops of the market demand. According to Economic historian Sudha Shenoy, 'Between 1730 and 1839, 4041 enclosure bills passed, 581 faced counter-petitions, and 872 others also failed' (Shenoy 2006). Small marginal peasantry and large section of rural wage labour could not buy the enclosure land because of high legal and other cost and non availability of the capital required for the commercial production. Against this acquired land, the small peasantry farmers were offered alternative land of inferior quality, with no access of water or wood. The impact of the enclosure movement was devastating because many small farmers, who are tilling on the infertile land, now could not produce sufficient and hence became near to landless. Also the mass agriculture labour which was dependent on these lands as source of labour also became unemployed. According to study done by J M Neeson, due to enclosure occurred from1750 to 1820, the small farmers from 30 per cent of

agriculture land were evicted and transferred to infertile land (Neeson cited in McElroy 2012).

The Enclosure Act was not a sole reason of marginalization of the people. There were series of other acts passed during the same time. Through these acts, the access of rural peasantry to '*open fields'* and '*waste land'* were restricted. The open fields especially were a source of livelihood for the rural peasantry. The open fields were the large agriculture areas to which all villagers had right to access and they used to divide it in narrow strips for the cultivation. The waste lands were barren land and usually were used for pasturing animals, collect firewood, fishing and harvesting meadow grass. In addition to this, people used to supplement their income by cottage industries, For example, weaving of wool. But after restriction was imposed on people access to common land, it became a reason of starvation of the people and especially rural labourer class which was majorly dependent on waste land. Also with an advent of cheap industrial manufactured cotton resulted in destruction of cottage industry and loss of supplementary livelihood (Hammond and Hammond 1987).

When access to the land was systematically denied by enactment of laws, the peasantry became helpless and remained with three options: to work as a tenant farmers for large land owners who had got land through enclosure act; to migrate to the new world; or to migrate to emerging cities of Industrial Revolution to fulfil their cheap labour demand (McElroy 2012). On the other hand rural labourer conditions were more deplorable and they remained with only one option of migrating to already crowded cities in search of wages (McElroy 2012). The 19th century conditions of the poor labour in the cities explained by Engels,

> The dwellings of the poorer classes are generally very filthy, apparently never subjected to any cleaning process whatever, consisting, in most cases, of a single room, ill-ventilated and yet cold, owing to broken, ill-fitting windows, sometimes damp and partially underground, and always scantily furnished and altogether comfortless, heaps of straw often serving for beds, in which a whole family -- male and female, young and old, are huddled together in revolting confusion. The supplies of water are obtained only from the public pumps, and the trouble of procuring it of course favours the accumulation of all kinds of abominations (Engels 2009: 29).

Hence the enclosure movement created displaced and disenfranchised new army of industrial reserved labour who were working for the starvation wages in the

industries. The socialist labour movement then aroused in the England which blamed the solely Industrial Revolution for the exploitation of surplus labour of masses. It is true that industry has exploited and still exploiting the labour, but one has to analyze the act in a context. It was a systematic process of marginalization and disenfranchisement of rural peasantry and labourer by denying their tradition livelihood rights to land in order to fulfil the demands of cheap labour of Industry (McElroy 2012).

3.2 Conceptual Framework: Expanding the Framework of Expropriation

In analyzing the phenomena in historical point of view, one has to analyze the historical means of expropriation. The current expropriation of human body cannot be seen separately but has to be seen as a continuation of the history. Hence the Marxian perspective of the process of expropriation was elaborated in the Section 3.1 of this chapter. As already discussed in that section, the land was a mean of expropriation in the eighteenth century Europe and hence there were attempts to grab the traditional land rights of masses. There is a gradual shift in the means of exploitation throughout the history. Starting from the period in Medieval England, through process of Enclosure movement, peoples land was grabbed for commercial production. The starving masses hence shifted to the cities in search of employment. The industrial capitalist then started exploitation surplus labour out of disenfranchised masses pouring in to cities.

In the historical expropriation of health of people, it is well known fact that in search of a new land, Europe has transmitted many diseases like kala-azar, bilharzias and cholera to the colonized population of North and South America, Africa and India (Shah 2006). They also imported African American people as slaves from the Africa. It resulted in transfer of African pathogens to America and resulted in the decline of about 90 per cent of the native population of American continent (Shah 2006). Land was the centre of exploitation as forests were cut down for more agriculture land and slaves were imported to work on the land. On the other hand, many local medicines were added to the western pharmacopoeia, for example from Brazil came the emetic ipecacuanha and from Peru came the tree bark quinine (Shah 2006). Hence in this era, good part of health of people from colonies was exploited to generate the surplus

capital. With the continuous drain of resources to the developed countries and later through the process of globalization, poverty has increased starkly in developing countries. During period of 1970s, it was realized that Fordist Manufacture had entered a period of irreversible decline (Cooper 2008). The Club of Rome's futures report of 1972, expressed the visible signs of crisis in ecological disequilibrium, slow down of economy, exhaustion of resources, rising level of pollution and famines. The report also pointed out that fossil fuels on which 97 per cent of industry including agriculture was dependent are exhausting very fast and soon economic growth will come to a halt. This prepositions lead to drastic changes in United States (US) economic structures through transformation from industrial to post industrial economy. The US moved out of manufacture based industrial economy to innovation based economy and it proposed the solutions to limits to growth predicted in Club of Rome report. The biotechnology and pharmaceutical industry shared a major part of this innovation based economy with a common ambition to overcome the ecological and economic limits to growth associated with the end of industrial production, through a speculative reinvention of future. Hence pharmaceutical and biotechnology industries restructured its growth model based on post industrial innovation based economy (Cooper 2008).

Since long period, pharmaceutical industry sustained its growth through innovation monopolies and patent protection. By 1970s, the generic drugs, especially from Indian pharmaceutical industry started flooding the market and it gave the big setback to the growth of pharmaceutical industry. On the top of that, after several clinical trial tragedies, government tighten the regulations on the clinical trials and hence resulted in slow down of research activity. Following these setbacks, around 1980s, the pharmaceutical industry started reorganizing its structures. They invested huge amount in new genetic technologies through investment in biotech firms or establishing own research units. Revolution in biotechnology and advances in genetic engineering resulted in a number of compounds that were coming out of laboratories, waiting to be tested for its therapeutic value. The stock of drugs in pipeline for trials was always maintained to sustain the investments based of hope and speculations (Cooper 2008). The major source of investment was through economies of innovation, scope and pre-emption. As Melinda Cooper said, 'it relies on the ability to anticipate the next wave, to keep ahead of the curve-than the economies of scale

associated with mass reproduction of commodities' (Cooper 2008: 24). Therefore in order to test the drugs in pipeline the locus of exploitation now has changed to ill health part of developing countries and has been looked upon as valuable to create market for new medicines. One of the researcher, Malcolm Potts[26] from the US expression looks at this phenomenon as obvious and normal. 'The real world is exceedingly painful, which means that the ill health of the developing world, which is now proving valuable for western science to mine, is something mournful perhaps, but as static and irreversible as the setting sun' (Shah 2006: 10). This has then followed by the globalization of clinical trials to satisfy the demand of bodies upon to test the drug which has been already discussed in the Chapter one.

The focus of this chapter is to further analyze the process of expropriation at next to global level. The analysis of the human research at institution level tries to analyze the individual behaviour in social, political, economic and cultural context. Healthy volunteers who volunteer to take part in clinical trials; the risk is very crucial and an important issue. In other phases of the trials, the participants participate in the trial with the hope of getting an access to free and new treatment, or take benefits of diagnostic facilities which are unaffordable to them. But in phase I trials volunteers are healthy. So it is very crucial to discuss as to why the volunteers are willing to take risks even after being aware of the adverse affect on their body. In a subset of healthy volunteers also, there are different categories like serial participants, professional guinea pigs and first time participants. The perception of the risk of these groups also varies with respect to their individual and shared experiences. For example, in the case of professional and serial participants, the routine of the participation normalizes the risk. But what plays a role in the case of first time participants? Is it only financial motive or peer group motive that makes them participate in the trials? These questions need to be examined in different approaches to risk.

Abadie has discussed the behavioural approach, cultural approach, situated rationality approach and political economy approach to risk (Abadie 2010). The behavioural approach to risk which was influenced by behavioural social psychology came mainly because of Human Immunodeficiency Virus (HIV) epidemic. It

[26] Malcom Pott is a PhD clinical researcher from US and his views has been expressed in the book *The Body Hunters* by Sonia Shah (2006)

established the direct relationship between individual knowledge and practices. Hence if an individual is informed with the correct information about the risk involved, the individual can take a rational decision about it. This approach still has its influence on the current discourses in the process of consent taking where underlying assumption is that if an individual is informed about the risk involved in study, he or she is rational enough to take decision about the participation. Critics of this theory argue that mere information cannot make an individual rational. Individual decisions are strongly influenced by social, economic, cultural and political context (Fisher 2013).

The cultural approach to the risk puts more emphasis on how risk is culturally, socially and historically constructed. So particular social groups and institutions share common view of perception about the risk based on the shared experiences among those social groups and institutions. Though this approach puts an individual in social context, it is very limited to social institution only and fails to address individual's interactions across the different social institutions which also influence his perception about risk.

The situated rationality approach gives more emphasis on individual's immediate surroundings which compels the individual to take decisions. It proposes that the individual weighs immediate benefits against risks involved and is forced to take a decision. Some of the examples of this approach are how present financial constraint wins over the immediate risk involved in phase I trial and how healthy volunteers underestimate minor adverse events like diarrhoea, headache. Most of the healthy volunteers take into consideration immediate risk while ignores long term effects of the frequent participation on their health (Abadie 2010). Critics of this approach say that it is influenced by individual rationality theory which fails to consider social process which influences the individuals' perception and assessment about risk. Apart from this it also highlights the present socioeconomic context and fails to address the historical context (Abadie 2010).

The political economy approach to risk is more focussed on how social, structural and historical processes has created the poor and disenfranchised people who are always the victims of risk (Abadie 2010). It tries to understand the process of industrialization, and how it undermines the workers safety and put them under

threat. It also tries to analyse and compare the vulnerability of healthy volunteers against other industry workers. For example, mining workers stays and work at a same place for longer duration. Hence they can share common experiences about their health problems and can relate it to the mining activity. But healthy volunteers stay at the trial site only during period of dosage and sample collection. Hence they lack the opportunity to relate shared experiences to the drug injected and hence underestimate the risk involved (Abadie 2010).

Fisher analyzes risk analyzes in terms of power asymmetry (Fisher 2015). According to this preposition, there is always lack of symmetry in the distribution of risk and there are always risk winners and risk losers. Pharmaceutical industry claims that it bears the risk of investing in a molecule till it is proven to be therapeutically effective. But the process of clinical research and approval of drug takes 12-15 years. As the pharmaceutical industry is not open to share data related expenditure on drug development, making an accurate assessment of costs is more difficult and hence pharmaceutical industry justify the increase in drug prices (Abadie 2010). 'The industry states that developing a new drug costs close to a billion dollars, whereas critics argue that costs are much lower and that significant amount are spent not in research and development but on marketing exercise' (Abadie 2010: 4) That is why in phase I trials, the pharmaceutical industry always wins while poor and disenfranchised always lose (Fisher 2015).

This study examines how the historical and present expropriation experiences normalizes the risk involved in phase I clinical trials. The generations of these healthy volunteers are experiencing number of threat and exploitation either in terms of state induced violence, caste, class, and gender based violence and every day struggle of survival. All these challenges have normalized the risk involved in the phase I clinical trial and is usually overshadowed by financial constraint. In a historical context, the study has tried to explore the phenomena of expropriation through historical shared experiences of the family members of the healthy volunteers. It is in the form of alienation from the land, caste and gender based violence, loss of traditional vocations and eviction of the slums. In a present form, the means of expropriation has just changed but the process is same and more intense. The commercial processes have entered into the lives of the people. The

pharmaceutical industry is encroaching at the micro-components in order to own the life at cellular level. It has made individual more vulnerable and marginalized.

3.3 Methodology

The main objective of this research was '*to study the historical and present expropriation experiences of the clinical trial participants'*. There is plenty literature available on the globalization of clinical trials and its impact on the population from developing world especially healthy volunteers. The objective of this research was to gather all these factors which have expropriated the bodies of healthy volunteers. It has also tried to incorporate the other phenomena of expropriation which are emerging through detailed qualitative studies in the Indian context. The research design hence adopted is a qualitative and exploratory where researcher will try to enlist all these factors which come under term expropriation in the case of healthy volunteers. Clinical research especially phase I trials in India are conducted clandestinely in the name of conducting ethical research and maintaining confidentiality of clinical trial participants. Therefore it is hard to find healthy volunteers who are participating in these trials. Snowball sampling method was adopted by the researcher to find these case studies. The researcher acquired the contacts of all the referred cases through a participant from Mumbai and an agent from Ahmedabad.

Total nine cases were interviewed comprehensively with the help of the interview guidelines prepared. Although as mentioned above, snowball and purposive sampling was used, the researcher has also tried to select the cases so that sample could be diversely represented based on variables such as women, severe adverse event (SAE) cases, Schedule Castes and Schedule Tribes, minorities and agents in clinical trial industry. The researcher has accordingly conducted a thorough interview of the healthy volunteers, three from Mumbai and four from Ahmadabad. The researcher has also interviewed two agents who are a husband wife duo who initially worked as healthy volunteers. Apart from the responses of the participants, the researcher has also noted down observations of the locality and the characteristics of the area in which the people live.

The researcher was introduced with first respondent called Ajay through one of a common friend. One of the researcher's friends was used to stay in the Gowandi slum, from where Ajay is belonged to. Researcher got the contact number of Ajay through that common friend. He was the respondent of the pilot study of the research. Initially, Ajay was in denying meeting researcher personally. But gradually researcher tried to develop rapport though different techniques like use of social media for the conversation, contacting through common friend. His house is in Gowandi slum where one of the Asia's largest abattoirs is located. The majority of the population is Muslim and most of the people from this slum are daily wagers and contractual workers. The condition of the slum is very deplorable just like the way Engels elaborated the nineteenth century England slums. The drainages were blocked; narrow roads; people running to catch local trains; and at least two to three drunkard sleeping on the roadside were some of the common view of the community. The housing conditions were very bad with many house ceilings were covered with tarpaulin sheets. According to Ajay, water drips in houses during heavy monsoon rain. The second respondent Rajesh, was Ajay' friend and he also lives in Gowandi slums. He is Ajay's school friend and Ajay introduced him to the researcher for a first time. Researcher got the contact numbers of Rajesh and another friend Iqbal from the Ajay and then he used same techniques to develop rapport.

During all three visits, Ajay was avoiding researcher to take him home. The researcher also never insisted about it but he himself once said that, his wife does not know that he participates in the study and he does not want her to know about it. Hence he cannot take the researcher to his home. Rajesh and Iqbal were more reluctant to meet. Finally it was decided to meet both of them together in presence of Ajay. The place of meeting was decided was Guru Teg Bahaddur local railway station. That was the only meet researcher could have with both of them.

In case of the respondents from Ahmedabad, the researcher got the information about some Severe Adverse Events (SAE) with healthy volunteers from Health Activists of *Swasthya Adhikar Manch*, a campaign against illegal and unethical clinical trials. Researcher got the contact number of the agent who is supposedly fighting for the rights of the victims of the clinical trials. Accordingly researcher called him and took an appointment to meet him along with all the victims of the clinical trials. On the day of visit, he suddenly cancelled the meeting saying that he is in the Surat. But

with continuous insistence on the phone, he was agreed to meet researcher. Accordingly on that morning, researcher went to an address given by him. The Vinoba Bhave Nagar is very much detached from the city because it is on the other side of the outer ring road. The distance from the city is almost 20 Km. The community is composed of migrant workers from different parts of the country such as Maharashtra, Karnataka, Madhya Pradesh and other parts of Gujarat. The workers usually travel to the city for daily wage work as well as some petty businesses and return to the community in the evening. Around 200 people in this area have been participating in clinical trials in different CROs in the city. Some of the participants have shifted to a locality called Amaraiwadi because they have been allotted a house under Rajiv Gandhi Awas Yojana at that location.

Overall it was very difficult to develop a rapport with respondents. There were enormous difficulties in the collection of data. The respondents were scared of seeing with researcher because they had fear that someone from the community who is also healthy volunteer will communicate to the CRO and they might discontinue him from the study. The respondents were frequently mentioning about some online database and if someone is blacklisted in that data base, it is visible to all CROs and then no one would recruit him or her. So researcher could not really develop rapport with respondents.

Table 3.1

Demographic Characteristics of Healthy Volunteers Interviewed

	Number (N)	**Percentage (%)**
Gender		
Women	5	55.56
Men	4	44.44
Age		
18-25	1	11.11
26-35	5	55.56
36-45	3	33.33
46-60		
60+	0	0
Caste		
SCs	4	44.44
STs	0	0
OBCs	4	44.44
Open	0	0
Religion		
Hindu	6	66.67
Muslim	1	11.11
Sikh	2	22.22

Most of the participants in the healthy volunteer category are *'serial participants'* whose participation is continuous and consistent. Most of the healthy volunteers are regular participants who look at the income aspect from participating as stipend or additional income to what they are earning from their usual job. Young male participant percentage is higher. The main reason could be self selection and larger friend circle which is primary informant of clinical trial studies. While in the after marriage phase, women participation is quite high and the reason behind their participation is either due to family debt or their husbands being alcoholic.

3.4 Ethical Considerations and Limitations

- The purpose of the research has been communicated to the respondents clearly in the languages they could understand.
- Informed consent form is prepared in Marathi and Gujarati language and consent has been taken with their signature on the consent form. Participation of respondents was voluntary and researcher assured them of right to withdraw at any stage of the study or can deny answering to any of the question asked which they do not want to answer.
- It has been assured to the respondents that the collected data will be solely used for academic purpose and confidentiality of the respondents will be maintained. During an interview, one respondent asked for help to write her complaint to Drug Controller General of India (DCGI) and researcher has helped her in writing that complaint.

During data collection for the study, the researcher has experienced number of ethical dilemmas and limitations. One limitation was regarding the access of data collection and rapport building with the respondents. The typical phenomena observed in clinical trial participants was, the one who has not faced any SAE or bad treatment from Contract Research Organization (CRO) were least interested in participating in this research. For example, three respondents from Mumbai and one male respondent from Ahmedabad were least interested as participation. Participation in the clinical trial has become profession for them and till now they have not faced any SAEs. Hence at the very first place, when researcher tried to

elaborate about the objective and purpose of the research, the healthy volunteers were not ready to participate as a respondent in the research. So it was needed to develop the rapport first. The researcher used different techniques to develop rapport to convince them to become respondents. The primarily there was an informal chat on the social media through smart phone which helped to build up the rapport. Then the researcher got the chance to meet them in person. The dilemma researcher here faced was, as at the very first place, healthy volunteers were not ready to participate in the research. Therefore researcher feels that the participation of these respondents was not completely voluntary.

Another dilemma related same group was while taking written consent. Two persons from Mumbai have knowledge that, if CRO found them giving interview for such study, they will be black listed and hence cannot participate in any trial then. Though researcher assured them of confidentiality, they were not ready to sign on the consent form as according to them signing the form, itself will disclose their identity. This issue has been primarily resolved by the researcher by building the trust through Ajay. But the interviews with these two people were not in depth because of only one meeting could be possible with them.

In case of other group of the respondents, who have either suffered through some kind of SAEs or the agent who have got bad treatment in CRO, were openly ready to participate. The objective of the research to find historical expropriation experiences of the respondents and their family members; and their current experiences in clinical trial setup. Hence major part of the questionnaire was intended to know about their family history and not related to problems they had faced in clinical trial setup. So researchers felt that, even after explaining the objective of the research, the respondents were finding the questions irrelevant to them as they were not addressing their issues. Researcher has always faced the burden of expectations of the respondents because respondents have a feeling that the person who is interviewing them will give relief to their problem. The words of one woman respondents who alleged that she had cancer because of the trial are very important in this respect:

> This incidence happened to me in the year 2012. Since then, number of media people, and people like you came to me asking what an issue was. They took my interview,

> publish the news in the media, but there is no change in our life conditions.... I expect you to write at least one complaint to the government on behalf of me (Heena Thakkar[27] February 2015)

Following this discussion, researcher tried to explain her that this is an academic research and research is a student. This research will not provide direct relief to her but will at least help in ice breaking the discussions on the rights of the healthy volunteers. As per her request the researcher helped her in writing complaint to the DCGI. But the question remained about the rights of the participants in getting help. The ethical guidelines for Social Science research in Health by Indian Council of Medical Research (ICMR) says about participant's right to get help as follows

> The researcher should try and get all the possible help that participants might require. The researcher also has a responsibility to help the participant(s) in cases of adverse consequences or retaliation against the participant(s) by any agency due to their participation in the research. Information, which may contribute to the improvement of quality of life of the participants, should be passed on to concerned person(s), official(s) or the agencies (Barai and Jesani 1998).

Though participants were not suffering through any health problem at the time of data collection, and the ICMR guidelines talks only about the situational conditions and relief, it raises a fundamental question that who will extend the immediate relief to respondents. What about their systemic issues which have not been addressed since ages? Are we generating social capital out of grieves of people?

3.5 Brief Summary of the Case Studies

The historical expropriation of the proletariat can be traced through shared experiences of their family members. It was the phase during which, the land of people in villages was snatched for the development projects, mining activities, industrialization and people were alienated from their land. Other different social and cultural factors also played a major role such as caste hierarchy and dowry system in dispossession of people from their land. It forced them to migrate towards the cities in search of livelihood. In cities, they usually settled either in slums of the heart of city or in the suburban areas. Rise in economic activity; commodification of premium lands in the heart of city and in the name of rehabilitation schemes of slum

[27] During the interview, Heena Thakkar has asked the researcher to reveal her identity as a participant.

dwellers like Rajiv Gandhi Awas Yojana, the poor are thrown at the periphery of the city. Poor in the city is always in a struggle to earn his livelihood, either through daily wages or petty businesses. While competing with the already established class in the cities, poor always lose the struggle for survival and become unemployed. At this juncture the only option they remain with is to commodify their lives. The clinical trial industry is one of the industries which demand such kind of hopeless and helpless people as healthy volunteers. The story of the respondents brings to light the process of expropriation through which propertyless and now lifeless proletariats are created.

Life in the village

"To experience real agony is something hard to write about, impossible to understand while it grips you; you are frightened out of your wits, can`t sit still, move, or even go decently insane"

-Charles Bukowski, *The People Look Like Flowers at Last*

Such is the agony and distressed situation in which the people that I have interviewed for this study are living in. The story of Ajay, Rajesh, Iqbal, Heena and Pallavi like people brings to light about the superficial world in which we people are living in. Human distress is real and very much existent in today's world. Who are these people who are living in such agony and pain and why? And why only them? What is the story behind this pain?

Ajay`s family came to Mumbai from the rural village Bhisada of Ghaziabad district, Uttar Pradesh with a dream to achieve heights and success as many others from rural India do. Village life has been hard on Ajay`s family specially because of their caste identity. They belonged to the caste Valmiki (manual scavengers), hence was Dalit by identity. Discrimination based on caste identity is a common practice in rural India and it is not surprising that Ajay`s family was also a victim of that. In a typical village life in rural India, in majority of the cases, land becomes the sole means of livelihood and survival. Thriving for survival becomes a difficult task without any adequate base of material support. Hit by acute poverty, every family looks for their own means of survival. Ajay`s father and his four brothers were having constant arguments over the four acres of land that they owned. Later, in order to end this

dispute among themselves, the five brothers distributed the land equally amongst themselves. With such hard life and bound by social discrimination, Ajay`s father decided to move his family to Mumbai in search of a better life, with a hope that Mumbai would do them good. It was a dream in search of a better means of survival. Mumbai instead of Delhi was opted because he was lucky to get a job as a ward boy in Nair hospital located in Mumbai. Migrating to Mumbai was a challenge but Ajay`s father took the step. They were allotted with a government quarter in Mumbai. The agony of the family of the Rajesh is same who lost their land in one canal project. It was time now to take a step further, to look forward for a better future. The challenges ahead seemed rough and difficult to overcome. But his father knew that this step was needed as their source of livelihood in the village is lost. Migrating to a big city like Mumbai from a small village in Rajasthan was a major step. After the small piece of land of his father acquired under the canal project his father got the compensation of rupees 10,000. Iqbal's story is a representation of the fishermen of the Mumbai and around areas. While sharing his childhood memories in the village, Iqbal shares the suffering of majority of the fishermen in and around Mumbai. According to him, around 50 per cent of the participants in CROs are from aagri[28] community and reason is that polluted water in Mumbai has destroyed their traditional fishing business.

> My father did not have enough money to buy a bigger boat for fishing in the deep waters, Fisherman in that area was no longer allowed to enter the estuaries for fishing. The estuary area was captured by the steel company for using it for carrying their raw materials in small boats (Iqbal February 2015).

Fishing was the means of livelihood for Iqbal's family. The coastal area of Alibagh, Raigad was the means of survival for so many fishing families. Families who could not afford to own big boats for fishing in the deep waters relied on the estuary for fishing with their small boats. Village life was simple with nothing much to expect but at least they were able to meet their daily needs. With the setting up of the steel plant, their only means of livelihood was disrupted. The sea water became so polluted in the estuary that fishing became a problem. They were unable to get a good catch. The only way out was to fish in the deep waters for which they required big boats which can sustain through big waves. Iqbal's father did try to fish with his

[28]Local fishing community

one boat for sometime but the income acquired was not enough to sustain his whole family. Unable to afford a big boat with the responsibility of looking after the family, survival had become difficult in the village overtime. Worry gripped him seeing the condition of the family, he had to find a way out. Until some few years back, life was difficult yet it was sustainable. With the steel plant setting up in their area, life changed drastically in a few years' time. Survival became a challenge. Iqbal still has flashes of memories about his village life, he felt nostalgic narrating the story about his village life.

The story of young married women Heenaben Thakkar, Snehalben, Pallavi and Savita brings to light the complexities of human suffering and the reasons entangled with it. Being born in a rural Indian village bound by social demands of traditions and culture brings in itself a set of problems of its own. Heenaben has three siblings, one brother and two sisters who are married and settled in Surat and Ahmedabad. Her father was a farmer and owned a small piece of land which was the means of livelihood for their family. Getting a daughter married in an Indian society is a big economic problem and Heena's father had the responsibility of three daughters on his shoulders. He had to sell off half of his land to get three of his daughters married. Snehalben, Pallavi and Savita belong to same caste called Vaghari i.e. vegetable grower and vender caste. Some of the sub-caste of Vaghari caste like Dantani used to sell toothbrush twigs. Sanehalben grew in a farm of vegetables and flowers owned by her father. She went to school till second standard. Her schooling was stopped after that because of the constructed social structure in their community whereby it is believed that girls should not go for higher education. Life in the village though it was difficult but still they were able to fulfil their daily needs through the income earned in the farm. The vegetables and flowers grown in their farm was sold to the local merchant which was then transferred to the market in the city. Her father had to pay an amount of rupees ten thousand as dowry for her marriage as is the tradition followed in many Indian families due to social and cultural demands. Pallavi got married at the young age of 17 years. She belonged from Kheda, a district in Gujarat. Their means of livelihood was cultivating vegetables and selling it in the local market. They owned a small piece of land. She belonged to the sub caste Dantani who were known by their occupation of selling twig brushes. But Pallavi narrated that she does not remember either her father or her grandfather doing this business.

Savita got married when she was nineteen year old and migrated with her husband to Ahmedabad.

Life in the city

Life in the city was not easy and it was full of challenges, everyday life struggle. Finding an affordable place to stay in a big city like Mumbai is difficult. Gowandi slum seemed like the right place to stay for Ajay and Rajesh's family considering the financial difficulties. Ajay and his three brothers and two sisters were born in Mumbai. With such meagre earning and a big family, survival had become difficult in Mumbai. Two of his brothers were employed as daily wage earners to support the family financially, one as a painter and the other work as a construction laborer. It was his third brother who worked in close connection with some Mafia gangs. Due to his involvement with the gang, the family was mentally tortured by police a number of times. The constant torture was becoming difficult to bear over time. It had affected his education in such a way that he had to drop out in standard nine. Over the course of years, Ajay's father had developed the habit of drinking alcohol which took his life. Ajay was a young man of 20 years old when his father passed away. His mother then took his father's place as an employee in the hospital to support his family financially. His brothers association with the mafia had pushed the family to such an extent that they had to leave the allotted government quarter and move to Gowandi slum where living was filled with difficulties. After two years of working, his mother retired from the hospital job. His two brothers had already extended their own individual families. All the savings that they had been doing for so many years was spent on his two sister's marriage. Crippled with no savings and no stable job, Ajay had to now look for a financial support system to support his mother and himself and hence he joined the job as a gym trainer.

Rajesh's father took one room on rent in the Gowandi slum. The plan was to set up a shop but since the rents was sky high for them, Rajesh's father decided to work in a shop for some time until he becomes financially stable to set up his own shop. Three years of his life was spent working in a shop. The income that he acquired through his small job was not enough to sustain his small family plus accomplish his dream of owning his own shop. Surrounded by these problems, in order to save money plus sustain his family, he went about running a small petty business near a beer bar in

Mankhurd area during the night time. His non-stop tireless double work earned him some good amount of money which he used to set up his own shop. The shop was doing good business due to which Rajesh along with his two sisters could also avail education. Rajesh narrated that it was not only his father but his mother was also equally involved in the small business that they were running. His mother use to help his father by preparing snacks to be sold at night near the beer bar. But tragedy befalls on the family when his father met with an accident which took his life. Rajesh was in tenth standard when this tragedy took place. Now with no earning member in the family to support them, all the financial responsibility of the family was passed on to his shoulders as being the only man in the family. After his first sister got married, he left his schooling to get himself involved in the family business. The responsibility of running the shop now rests on his shoulders. Since the family was in a heavy debt after his father's demise and the income acquired from the shop was not enough to cover the costs plus pay off the debt. Hence, with a heavy heart Rajesh decided to close down the shop and work as a contract labor in a mechanical industry. His marriage after two years only added to his agony. He had to take loan for his marriage which added to his already existent misery. With a loss of traditional fishing occupation, Iqbal's family shifted to Mumbai helped by one of his uncle. His uncle helped his father get employed as a daily wage earner, his father now earns an amount of rupees 350. Iqbal has three siblings, one elder brother who is working as a painter and two sisters who are married. He said that they still has their house in their village which is being used by one of his uncles.

. Anil Keshwani and Seema are two agents who have been involved in the business of clinical trials as agents for the past four years. They recruit people from Vinoba Bhave Nagar, Gujarat from where they belong from. They are also involved actively in recruiting women for surrogacy and egg donation. Anil's family is Sikh by religion. His ancestors migrated to Gujarat looking for a better livelihood. His father worked as a mill worker in Ahmedabad and his mother ran a petty business to support the family financially. With the rising expenses of everyday life, it was becoming difficult to provide ends meet. House rents had increased to such an extent that it had become unaffordable over time and hence Anil's family had to shift from the central city near the railway station where they were staying to the outskirts of the city looking for an affordable rent. Central city is flocked with migrated people

looking for jobs or trying to set up their own business therefore there are better opportunities for small businesses in the outskirts of the city Anil added. He studied till tenth standard and set up his own business, a small saree shop. His wife is basically from Punjab and shifted to Ahmedabad after marriage. They have two children, one son who is in tenth standard and a daughter who is married.

Heena shifted to Vinoba Bhave Nagar in Ahmedabad after marriage. She lives with her mother-in-law and husband. She has three children. Her husband is an auto-rickshaw driver and earns four to five thousand per month. From that small amount, her house rent amounts to rupees 2000 and another amount of rupees 1500 is given as rent for the auto. Initially, they were settled in the heart of the city in an area called Saraspur but with increasing economic difficulties they had to shift to the outskirts of the city. Feeding a family of six members along with additional basic needs of everyday life became a difficult task for Heena's family. They had no choice but to take loan from the local money lender at a high interest rate of three to four percent which amounts to about 36 per cent in a year for meeting their basic needs like medical emergencies and school fees.

Snehalben lives in Amraiwadi, a suburb area in Ahmedabad with her husband. They do not have any children. Her husband was working as an auto rickshaw driver. His travel route was Jashoda Chowk from the main city to Vinoba Bhave Nagar when they were living in Vinoba Bhave Nagar. His income was just rupees four thousand per month. In that amount rupees one thousand was given for house rent and the rent for auto was rupees 1500 per month. The remaining 1500 rupees was used for daily expenses which was a very small amount to cover even their basic expenses. Things started to worsen when his husband met with an accident due to which the auto owner decided not to employ him anymore. With her husband unemployed there was no source of income to survive. With no way out, they took loan from the money lender with a very high interest rate. Her husband then started working as a daily wage earner. On top of that, her husband developed the habit of drinking which only amounted to the already heavy debt. With the debt amounting to rupees 75,000 and no money to pay back, the money lender started harassing her.

With the money that they had acquired through from selling their small piece of land plus loan taken from the money lender, Pallavi and her husband started their own

vegetable vending business. Pallavi further explained that all the vegetable vendors in Vinoba Bhave rely on the local money lender to sustain their business. The benefit of such loans is that short loans could be taken easily for a short period of time against jewellery or other valuable goods. The interest rate is very high at which this loans are available. With interest rates increasing and poor income, the debt had amounted to rupees 15,000.

As like in case of Pallavi, Savita's husband was also under debt and became alcoholic. He used to earn around 150 rupees daily out of which half money he used to spend for alcohol. He was not looking after her and hence Savita used to take loan from money lender for purchasing household needy goods. In the year 2011, her child was two year old when she got sick because of hepatitis. She was serious and hence they admitted her in LG hospital for the treatment. Even though it was a government hospital, she spent around 70-80 thousand rupees for her treatment. The debt on family increased tremendously and the money lender was torturing her. It was very tough time and at the times, she got feeling of committing suicide out of helplessness.

Expropriation in Clinical trial setup

This is how the financial constraints and daily struggle for life forced the healthy volunteers to get introduced to the clinical trial industry. Ajay was introduced into the business of earning extra money through participating in drug trial through his brother who was already involved in it. In the initial stage, Ajay was sceptical about this step due to the number of news that he has heard about SAEs in participating individuals but later on eventually burdened with responsibility of supporting his family financially and attracted by the livelihood of his friends from the same community who were participants in the trials, he decided to step into it. He was also further convinced when one of his friend told him that he had personally visited the Contract Research Organization (CRO) where the people employed out there had convinced him that this test are safe and that the medicines that are being given to them have already been launched in the market and even if it is a new drug that is being used, it is completely safe. They also told him that it is just a simple official procedure that they need to follow for marketing the medicines. In the first trial in one of the CRO from Panvel, Mumbai, he earned an amount of rupees 6000.

Experiencing of owning such a big amount of money for the first time for just one trial, he spent his money on material things like clothes and alcohol. This amount had attracted him to participate in more trials moving from two times to sometimes three times. Later his body started showing symptoms of illness like skin disease, weight loss and diarrhoea. He testified that since during that time there was no official procedure of online database for trial participants and recording was arranged only in simple manual register. This gave them the leverage to participate in more than one trial. The more he became financially stable through participation in different trials, the more he got over his fear and anxiety. The ambition to have a better life like others and to financially become independent, had pushed him further into this business. His marriage in 2011 and the fear that was he would turn impotent if he keeps on continuing participating in the trial by some his friends had encouraged him to leave the trail for a year or two. But the added responsibility after marriage and the demands of everyday life pushed him into the business again. Surviving in a city life Mumbai is very difficult even for a middle class family. And Ajay was just a gym instructor earning a meagre salary of 2000 to 3000 rupees. How was he to manage his family with such a small amount of money? His house rent only amounted to rupees 3000. With added necessity of survival, it became impossible. He had the responsibility of taking care of his mother and wife plus a dream to extend his family further. Such is the level of helplessness that so many people are living in that push them to take up such harmful step. The more the risk involved in this business, the more money you earn. His testimony also highlighted one certain incident where three participants lost their lives and one went into coma while the trail was being conducted, the lab where the mishap occurred was in one of the CRO from Rabale, Mumbai. He also shared one of his experiences where he and his friend had gone to one CRO from Andheri, Mumbai, for a trial of psychiatric drug where they were offered Rs.10,000 for one trial. The medicine given was a 25 mg tablet, which after consumption, their blood pressure started rising. They contacted the doctor from the laboratory but the doctors refused to take any responsibility and advised them to get it checked by a local doctor.

It was during the period of suffering from heavy debt that Rajesh was introduced of earning extra money through participating in clinical trial. This information was brought to him by one of his friend in the neighborhood. Like everyone else he was

also sceptical about involving in this business but later on pushed by so many difficult factors he had to indulge himself in this business. He testified that till date he has undergone sixteen trials. He narrated that all SAEs are not true and that most of it is imaginative. He added that these experiences occur because you tend to feel the same physical problems after listening to a friend who has undergone the same trial. He meant that it is mostly psychological. He further said that minor adverse reactions are felt like headache, diarrhoea occurred but they can be cured by medicines from local medicine shop. Due to these extra earnings, Rajesh was able to pay off his debt. He still continues to go for trial once every month. Life in Mumbai is very difficult, Rajesh added. He wants to own a grocery shop but for that he needs to save a good amount of money. Owning a job which offers him only a small salary does not help him to survive in a big city like Mumbai. Hence, clinical trial becomes an extra earning source even though dangers to life are involved. Iqbal has participated in eight trials so far and he is proud to be independent financially. All his earnings through those trails are spent on material things. His family is not aware about his source of income and he intends to keep it like that for the moment. Iqbal further added that about 50 per cent of the participants in the CROs are from aagri community and shares the same story with his family. Sea water pollution through setting up of plants has destroyed their only means of livelihood and hence in search of income, they have no way out but to shift in cities like Mumbai and look for jobs through which they can atleast survive. Iqbal is 21 years now actively involved as a participant in clinical trials and his father works as a daily wage earner in Crawford market and mother works as a sweeper. A number of families have been pushed into such distress conditions because of such plans.

Anil and Seema who are agents recruiting healthy volunteers in clinical trial industry came to know about this form his known associates working in a wholesale market in Surat. He then searched for research centres carrying out this same kind of trials in his hometown Ahmedabad and enrolled himself for the study. He then enrolled his wife in another study. So far, his wife Seema has participated in 27 trials and himself in 14 trials. They were overwhelmed by the earning that they received that they started working as agents for pulling in people for participating in the trials. They received rupees 100 to 400 per person as incentives. They used their shop as a means for attracting people into this business. They convinced people coming to their shop

for buying sarees. So far around 200 people are undergoing trial through them. Anil gave out some detailed information about the CROs in which he is associated with. He said that there are no fixed criteria for hiring an agent. Anyone who brings in people to participate in the trail are given the particular amount irrespective of where they come from or who are they bringing? The CROs are target oriented, they do not care about the ways in which the participants are coming in. he further added that both the CROs and the participants use illegal means to enrol in two trials at a time. They manipulate the required official procedure whereby they are asked to provide their identity proof which is uploaded in the online database for recording. In this way for every trial that they undergo their name is recorded in the online database for scrutiny. People use various means to over pass this procedure by providing different identity proofs for different trials. These CROs are not doing genuine research according to Anil said.

When Heenaben came to know about the clinical trials, she got attracted to the means of earning money through it. She thought she will participate in one or two studies and clear her loan of Rs15000. She has participated in two trials till date and after being diagnosed with brain cancer during the second trial, she has completely stopped participating. The study was conducted in the year 2012 and she has preserved all the bills of her treatment and her copy of the consent form of that particular trial. The particular study was conducted in two parts with periodic sample collection of the blood and urine. During the first part of the study, they gave her one tablet twice a day for three days. Apart from that they use to collect her blood and urine samples as well. After completing first part, when she came back home, she suffered from minor headache. After 25 days, when she went back for completing the second part, she complained about the headache to the doctor from the Clientha Research organization but the doctor said that it is a temporary effect which will last for a while and disappear. After completion of the second part, when she returned home, she suffered from severe headache and had a spell of headache where she had lost consciousness. Her husband immediately called the research centre for help, to which they did not respond. Hence he personally visited the centre along with his wife but he was not allowed to go inside. With no option left, he took her to Lallubhai Gordhanbhai (LG) hospital which is a government hospital and doctors were inattentive to their complaints. After several tests, it was diagnosed that his wife

had brain cancer. Doctors in the LG hospital suggested him to shift her in the Civil hospital, Ahmedabad where she had been operated. The cost of treatment, medicines and tests came to around one lakh. The initial debt of 15 thousand for which she had participated in the trial has now been added up to one lakh. Her children have stopped going to school. Her mother in law is now participating in the trials and her husband is working hard to pay back the debt.

Burden of debt and alcoholism of his husband forced Snehalben to participate in the trials. She started earning money through participating in clinical trials. The period of trial lasted from two to three days. She decided not to tell her husband about this due to his addiction. She gave the excuse that she was going to her mother's place to her husband whenever she had to go for the trial. Since this visitation started happening frequently, her husband became suspicious and wanted to check on her. On one such occasion her husband went to her mother's place to confirm his doubts. When he found that she was not there, they had a big argument. She was beaten up badly. With no choice left she had to tell her involvement in the clinical trial to her husband. When he learned that she has been earning a lot of money through the trials, he started harassing and physically abuses her for money. Over a period of one year, she participated in over 5 trials. On her sixth trial, she was given a compensation amount of rupees 10,190. The arrangement for the trials was done in such a way that transportation was provided by the CROs. In her colony, a vehicle was provided to pick up all women who were ready to participate. At that time, one vehicle came to Vinoba Bhave Nagar to pick up women who all were ready to participate. She successfully completed part one of the study in which they took around 500 ml of blood in a period of two days. When she went for the second part of the study after 25 days, during primary blood test, the test reported that she was pregnant. When she denied of going through an abortion as advised by the employees of the CROs, she was threatened that she had to abort since she had already gone through the first phase of trial, there was a chance that the baby would be born with disability. The CROs could not afford to ruin their reputation by such cases. It would have been harmful for the company. And hence she was convinced to go for the abortion. Two tablets were given, one was taken in then CRO and the other was taken at home. When she started having severe abdominal pain, her husband who was unaware of the abortion took her to the CRO for treatment. In the CRO, the husband learned

about the abortion. He was so furious to hear about the abortion which she did without his consent that he started quarrelling with her in the CRO itself. After that incident, her husband started torturing her every day. Unable to tolerate the torture anymore, she divorced him. Currently she is staying with her mother.

Pallavi learned about the clinical trial and the money that can earned through it and enrolled her name for it. Even after paying off her debt, when she felt no harm in her body after the first trial. She continued to participate. In her eight trial she received a compensation of rupees 10,190. She testified that during a trial her test report stated that she was pregnant. This incident happened in the same time like Snehalben of the earlier case explained above. Her first test before the report of pregnancy where they took 500ml of blood in a period of two days was successfully completed. It was the second part of the test after 25 days that she received her report of pregnancy. Pallavi also had to go through the same situation like Snehalben where she was also convinced to abort by the CRO staff. After taking the second tablet, the pain in the lower abdomen started and her husband took her to the CRO. Her husband knew about the situation and hence did not create any problem. After the abortion, CRO representative denied to give her remaining compensation amount with the excuse that she did not complete the study. They even denied to give her copy of the consent form.

The composition of the participants is mixed group of both middle as well as lower class people. On being asked whether there is any differential treatment given based on class, he said that such discrimination does take place. The doctors and nurses behave differently with the lower class people. The actual drug trial starts where the dose of the trial medicine is given to the participants either in the form of a tablet or it is injected. Sometimes participant act like they have swollen the drug and after nurse goes to next participant, they throw the medicine in the dustbin. Sometimes it also happens that participant does not like the taste of the medicine and hence vomit the medicine right after swallowing it. As one dose is spoiled, the person who has vomited has to quit the study. Each study mentions about the quantity of blood loss during the trial. Right after the dose, the blood is taken for an analysis after certain time interval which is mentioned in the study protocol. The usual procedure is to take 3-4 ml blood hourly. One has to strictly follow the given diet and schedule which is also mentioned in the consent form. Every activity is observed through a close circuit

camera and even urination is not allowed without permission. The main complaint participants had was about the food served which is not good and in some labs the food is not even hygienic enough to be consumed. But one cannot question or complain or even ask for more compensation in case of severe adverse event because then the CRO will blacklist his or her name which is shown to all the CROs since they have an online common database. Ajay shared one such incident from one of the CRO, that 12 people from Ahmadabad mostly youngsters had come for clinical trial in this CRO and after injecting trial medicine, their hands got swollen. The infection was so severe that their hands had to be amputated. Each of them got a compensation of two lakh. After listening to the incident the researcher asked him, whether he still wanted to go for the trials or not to which he replied: "For the poor every day is a day full of risk, uncertainty and a gamble. Our day starts with only one aim i.e. to feed our family and self. This kind of incidents doesn't happen frequently and I am ready to take the risk for the money I can earn which can feed my family."

The agent usually contacts them through phone, WhatsApp with listed contact numbers of the people who are serial participants. The agent takes Rs.100 per patient from the laboratory. As per the rule such clinical trial usually has its inclusion criteria but in these laboratories, even though the person is out of the inclusion criteria (Blood Pressure, Diabetic), the agent allows him for the trial for which he takes Rs.1000 from the particular person. Anil said that in order to avoid this check, people produce fake identity proofs and the CRO representatives have no problem accepting such fake identity proof. Women usually can produce two identity proofs: one before and one after marriage both having different surnames so an online database cannot detect it and women can participate in two trials at a time. According to him, CROs are not doing this job to conduct proper research and produce genuine data but just to achieve the target sample. Participants also use different techniques like rubbing ice on syringe marks so that CROs cannot recognize their involvement in another trial. There are some CROs who, without hesitating, accept participants who have already participated in the other trials. He also mentioned about one CRO affiliated to Sun Pharmaceuticals in Baroda, Gujarat, where people are recruited without any protocol. According to him, exclusion and inclusion criteria of studies are not followed and beggars on the streets, alcoholics, drug addicts and handicapped people are picked up from streets and slums and put on trial. He also said that, there are some risky trials

for which local participants from that city are not ready to participate therefore sometimes they have to send participants to distant places like Mumbai, Hyderabad, Bengaluru. If the trial location is outside Ahmadabad, agents get Rs.400 per participant that means Rs. 200 extra. Also CROs arranges all the travelling and accommodation for all the participants. In Hyderabad and Mumbai, they have rented flats where participants can come and stay during the period of trial. When researcher asked that in spite of the bad treatment from the CROs and SAEs in women why they are still pursuing this profession, Seema said that, 'no all studies are bad. We usually manage on ourselves when there are some minor adverse reactions like headache, diarrhoea. But our main demand is that when there are such kinds of SAEs, the CRO should take responsibility of the participants'.

Nowadays some CROs are sending messages in bulk to mobiles numbers in their database. Apart from that one directly call the particular laboratory and enquire about any ongoing study which needs recruitment. Anyone can also go with their friends who have received the message stating the study details. If a particular participant is married, the CRO representatives also ask whether their wife and children could participate. If the trial participant is exclusively meant for a child they offer more money sometimes even 15-20 thousands. If one person calls the agents, they are given the location, date and the time of the trial. In one hall, there are about 50-60 volunteers. All kinds of people especially Aagri communities (Fishing communities) usually come for the trial. Firstly, they examine the body, take blood sample, urine for the purpose to check whether the person is in the inclusion criteria of the trial or not. According to him, all these tests are manipulated and they accept everyone who has given their consent to participate. They are given a bunch of papers of about 15 pages where the information about the trial medicine has been mentioned. They give one hour time to read all the information in the hall where no one is present except the volunteers. If one agrees and sign on the consent form then that person has to remove the clothes, submit all the belongings along with the mobile phone and keep them in the locker of laboratory. They don't even give the participant's copy of consent form. It is given to the participants only when they complete all the visits. The trials are completed in two to three visits. This means once a person participates in the trial, he has to go every Tuesday to the laboratory for second and third visit when again some medicine will be given to be consumed and hourly blood samples

are collected. The stay in the laboratory may be from one to three days. People usually get Rs.5000-20000 after the completion of all stages. It has been stated in the form about the amount to be given after completion of each visit which is exactly given to all the participants.

3.6 Findings and Discussion

3.6.1 Expropriation Experiences of the Healthy Volunteers

The expropriation of the healthy volunteers can be seen in many dimensions. One could be historical socioeconomic exploitation of generations of some class, castes, gender and shared experiences of the family members can be a source of the information. The other kind of expropriation is experienced by the healthy volunteers but outside the clinical trial setup. The third dimension of the expropriation is the exploitation of the healthy volunteers within clinical trial setup.

Through analysis of the shared experiences heard by the healthy volunteers from their family members, it can be observed that there is a historical exploitation of the certain castes, class and genders. Taking an example of the first case of Ajay, his caste is Valmiki i.e. manual scavenging caste. Though he has actually not worked as a manual scavenger, he has a memory of shared history from his parents of this dehumanizing work.

In India, manual scavenging castes had given the role of picking up the human excreta from upper caste houses and dump it outside the village. This dehumanizing work they are doing in exchange of some remained food and clothes offered by upper caste. This feudal oppression designed by caste oppression has kept many people subjugated for generations. The stigma experienced by the manual scavengers is very painful. For hundreds of years, they were not allowed to enter homes through front door, not allowed eat food with upper castes and treated as untouchables. Following the struggles of Safai Karmachari Andolan and battle in a Supreme Court of India, the law was passed by Parliament by enacting *Employment of Manual Scavengers and Construction of Dry Latrines (Prohibition) Act, 1993* (Singh 2014). Almost 25 years after the passage of the law, still manual scavenging is the reality of Modern India. The recent Socio-economic Census data revealed that still there are

around 1.8 lakh manual scavenging households in the country (Venkat 2015). The current trend of number of manual scavengers shows that the number is decreasing and it may be attributed to the migration of the people of this caste to urban centres in search of new opportunities. Here they found some job as a daily wager or contractual labour which also exploits them economically, but the nature of work is not dehumanizing up to the level of manual scavenging. In the case of Ajay, the body commodification in clinical trial setup is exploitative but when he will compare it with the sufferings of his forefathers, it is more dignified in his perspective.

In a peculiar case of Iqbal who shares the experiences of the fishing communities in Mumbai and nearby area, the impact of industrialization and ecological destruction resulted in loss of livelihood of the fishing community. The accounts of the famous Marathi writer, Milind Bokil are representative of this fact. The establishment of the steel plant and other industry near seashore in Mumbai and neighbour districts resulted in severe ecological destruction and pollution. The community rights of the fishing communities over sea and estuaries were abandoned and their movement in the sea was restricted. The estuaries were opened to the transportation of the raw material on boats. It resulted in destruction of fishing nets of the fishermen. The pollution of the sea and estuary water resulted in destruction of agriculture and fishing. The livelihood of the fishing community came under threat and ultimately many people of these communities migrated to nearby Mumbai city in search of livelihood (Bokil 2006).

Other three women who interviewed from Ahmadabad were of Vaghri caste. The Vaghri are divided into a number of sub-divisions, the main sub division are Chunarias, who are cultivators, the Datanias who sell twig toothbrushes, the Vedus who sell gourd, Salaat, who are stonemasons, and the remaining castes being landless agricultural workers (Lal and Singh 2003). All of three women respondents were of Dantania sub caste. It is well known fact that how the rights of the adivasis and other communities over local resources have been abolished by the state. The process of globalization has its impact on the village level micro industry and vocations. The Dantannias who were selling twig toothbrushes lost their vocations and had to migrate to urban centres to earn their livelihood.

The other phenomena which is coming out of the interviews is that total seven participant's families were connected to agriculture or other activities in villages. The different social, economic and cultural processes have forced them to migrate to cities. The families of the participants were expropriated from their land through socio-economic and cultural processes resulted in loss of the livelihood. In the case of Rajesh, his forefather's land was acquired in the canal project. In the case of women from vaghari community, their families had to sell part of their land for the dowry in marriages of their daughters. In the case of Ajay and Pallavi, the land owned by the family was very small and after expansion of the families, they had to sell their land because the production was not sufficient to sustain expanded families. Ultimately they forced to migrate to the cities in search of starvation wages.

People migrated to the cities with a hope of opportunities of livelihood, but here also they faced the expropriation of their labour from already established class. If we observe the daily wages of the respondents or their family members, they are very much near to minimum wages of urban localities. The father of Iqbal earns only 350 rupees per day, the vaghari women's husband could only save 100-150 rupees daily and an auto rickshaw driver remains with 1000 rupees for his household needs per month. This explains how people's surplus labour is exploited and if any health or other emergency occur in the family, they just left with borrowing loans from local money lender. The poor from the cities were also ousted to outskirt of the city. Two respondents and their families were initially living in the centre of the city. But due to rise in the house rents, demolition of slums in the name of development activities and in the name of rehabilitation poor in the slums, they were allotted the houses at the outskirt of the city or forced to migrate to the semi-urban areas.

Another crucial issue with the petty businessman in the urban localities is availability of loan. The problem with most of the labour from unorganized sector is they do not have a consistent income because most of them work as daily wager or contractual labour (Jeelani 2015). Even after producing proofs of consistent income, the banks perceive them as a poor applicant and reject their loan application. According to one report published by Housing Bank of India, around 80 per cent of the economically weaker section does not have access to the institutional loan (Jeelani 2015). Therefore ultimately they remain with an option to take loan from loan money lender at high rate of interest. In a case of women respondent from vegetable vender

families, they took short loans from local money lenders for their petty businesses and medical emergency in the family. They are paying the interest of three percent per month which is almost 36 per cent per year. It results into inflated loan amounts and family unrest. In case of non-payment of the monthly interest, that amount adds up into principle amount and debt amount increases at tremendous pace. In a case of these women healthy volunteers, the money lender was threatening them for non-payment of the loan. Therefore women in this condition were forced to participate in such trials.

Apart from this kind of threat, the poor people have seen and suffered a lot of body violence through generations either externally or internally. Two women mentioned in the studies i.e. Pallavi and Snehal were beaten up by their drunken husbands. In the case of Ajay from Mumbai, his family members have been harassed by the police on the suspicion of his brother's linkages with mafia in Mumbai. Apart from this, either directly or indirectly, they and their generations have experienced a lot of bodily violence.

It is not only the uncertainty in livelihood but non-responsiveness of the other systems also forces the poor towards marginalization. In a case of Heena, her perception is that the trial causes cancer in her brain. But when CRO denied taking the responsibility, she approached the government hospital for treatment. Even though it is a public hospital, she spent more than lakh rupees for her treatment. Apart from that, doctors were less attentive and did not handle the case sensitively. This caused her to borrow loan and now she is under debt of 1 lakh rupees. In another case of Savita, her girl child was suffering through hepatitis and for her treatment they spent almost 70-80 thousand rupees. Inadequate and non-responsive public health services forced these women to participate in the trials.

Another component is expropriation in the clinical trial setup itself. If we analyze this in an economic point of view it is very distressing to see the human bodies being commodified. In the developed countries like USA, people with diseases do participate in the trial because they think they will get some advanced treatment for free or at minimum cost. The diseases are rare and in these cases the patients themselves take the decision to participate in the trial after understanding the sufferings and are aware that no treatment is available for the disease they are

suffering from (Shah 2006). But in a country like India, poverty is so prevalent, general health services are poor and treatment in the private sector is unaffordable. The poor people are lured by researchers to participating in the trials by offering them financial incentives and free treatment. There are incidences in Indore, Madhya Pradesh, where doctors have lured the patients by giving wrong information. For example, doctor said that it is a government project, this is more advanced treatment, promise of free of cost treatment (State Economic Offences Investigation Bureau, Madhya Pradesh 2011). Hence informed consent is itself a crucial issue in the case of India. But the condition of healthy volunteers is more deplorable where they have to consume the trial medicine which they do not need and hence it is like you are commodifying your body just for the sake of getting financial compensation. There is also a difference between the people who sell their body organs, professional blood donors and professional guinea pigs because in the former case the only part or parts of body are vulnerable and commodified while in the later the whole body is at the state of risk and commodification (Shah 2006). If one analyzes the transactions between the healthy volunteers and CRO without considering the social, economic, political and cultural factors, it is seen as fair and normal transaction. In an informal interview researcher was explaining the issue to a friend[29] working in one of the CRO from Mumbai to which he replied, 'so what? In the exchange of their bodies, they are getting money. So where is the problem?' As Karl Marx says, 'A commodity appears at first sight an extremely obvious, trivial thing. But its analysis bring out that it is a very strange thing' (Marx 2013: 46). As in the case of transactions being done in the clinical trial setup, one need to understand that the body of healthy volunteers is commodified at the micro level. The analysis of the system at policy level, institutional level and cultural level, shows that the neoliberal phenomena is commodifiying every part of the body.

The desensitization of the pain has not only taken place with the participants but also with the investigators and nurses who have became the puppets of the pharmaceutical industries and are blindly following what has been mentioned in the research methodology in order to complete the study. In the case of a woman who suffered through cancer, the CRO staff's behaviour was insensitive and

[29] He is a researcher's friend working in one of the CRO from Mumbai and gave an informal interview to researcher in January 2015

nonresponsive to the victim needs. On the contrary, there are some researchers who are very much responsive to participants needs. In the US, there are incidences when investigators have rejected the studies which might cause pain, irrational with respect to condition of the patients. Bradley Logan[30], MD from US rejected the study which requires surgical insertion of telescopic device into the women's abdomen which was bigger than what he had been using long time back (Shah 2006).

3.6.2 Motivation behind Participation and Adherence to Study

There are many studies which have listed the motivation of participants in the clinical trial studies and they are altruism; financial compensation; and hope of access to promising treatment (Edelblute and Fisher 2015). In case of phase I clinical trials, the participants are healthy volunteers therefore hope of access to promising treatment cannot be a motivation to participate in the trials. The other two could be the whole or partially might be the motivation behind the participation. In this study, only one respondent mentioned altruism as the motivation while remaining all the remaining eight respondents mentioned financial compensation as a primary motivation. The respondent who mentioned altruism as a primary motivation is currently not working as a healthy volunteer but as an agent. Therefore it can be concluded that most of the research participants in the phase I trial are motivated by a motive of financial compensation. But altruism has been considered as an important motivational factor in a context of clinical trials. Some people even evaluate the ethics in the research based on evidences of how much participant is motivated by the altruism (Fisher and Kalbaugh 2012). In India, there are several issues related livelihood of the people. Most of the agriculture labour and labour from unorganized sector works at minimum wages. The community rights on land, forest and water are shrinking and more land is being privatized to exploit the resources out of the land through commercialization of agriculture, mining activities and industrialization. There is also large chunk of youth who is unskilled and unemployed. Despite there is issues like inadequate public health services, unaffordable cost of treatment in private health care setup. There are also power dynamics in doctor-patient

[30] Bradley Logan is a MD from US and his views has been expressed in the book *The Body Hunters* by Sonia Shah

relationship and information asymmetry always does exist. These factors make participants more vulnerable and can be easily lured for participation in the trials. So it is very hard to find an individual who is motivated to participate in the clinical trial with altruistic motive and wants to contribute to medical knowledge. Though altruism is not an initial motivation for participating in the research, the researchers have another opportunity to develop altruism at the time of initial screening of healthy volunteers or during the study in order to conduct the ethical study. Even though motive behind the participation in the study is not altruism, it's the primary responsibility of the principal investigator, research coordinator and nurses to teach altruism to the participants. It can be said that it is a required process for the researcher to develop a feeling of altruism in order to sustain the participation of participants. In the case of developed countries, different studies tells us that research co-ordinators play a larger role in developing altruism in the participants during different stages of research (Fisher and Kalbaugh 2012). As one of the co-ordinator in US explains,

> There are very few people that enter our studies that are altruistic, except at the end they really become altruistic because we try to teach them what research is about, it's not about being a hamster and you join a study. You want to learn...why this is done, what the principle behind is, and at the end, they're like 'Wow, I really helped some other people. ''Yeah, you have. 'But they didn't [think] that, typically, going in. (Fisher and Kalbaugh 2012: 146)

This kind of altruism in induced kind of altruism with self interest. Jill Fisher describes about three self motives of research co-ordinator and nurses to produce altruism in participant (Fisher and Kalbaugh 2012). First one is to motivate participants to be adherent research subjects by underscoring the *'right'* reasons to participate in clinical trials, especially their contribution to science and society; second is to minimize tensions they experience in this work between research and care; and last one is to contest the undervaluation of their work. Haigh termed it as *'Selfish altruism'* or *'survival of the group'* (Haigh cited in Fisher and Kalbaugh 2012). But in the Indian context, threat is used to sustain the participation. The power dynamics between the CRO representatives and healthy volunteers does exist and according to Rajesh, whom researcher have interviewed the CRO representative always makes feel the healthy volunteers that they are at receiving end so should listen to whatever CRO representatives are commanding. Someone cannot question

the process of consent taking or even subsections of the study. For example, if you are questioning about any part of the study the threat is made of withdrawing from the study is given. As one of the respondent quotes,

> You cannot question them. Once one of my co-participants questioned about the post trial severe adverse events of psychotropic drug and in response they threatened him that they will throw him out of the study and won't give the remaining compensation (Ajay, 17th November 2014).

In fact the large instalment out of the compensation amount is given at the end of the study in order to make the people adhere to the study. Below is one section of the copy of consent form which shows out of total compensation amount Rs. 9550, larger instalment that is Rs. 7550 is given after completion of the study. Hence one has to adhere to the study in order to get full compensation amount.

Figure 3.1

Different Slabs in which Financial Compensation Paid

What are my financial benefits?

You will be offered a compensation amount for you participation. This compensation amount will be decided based on the rules prescribed by Ethics Committee members. The Ethics Committee has already evaluated and approved the study. You will get the compensation of Rs.9550/- which will be given in instalment described below.

Sr.No.	**Visit**	**Amount**
1	Time Period-1	500/-
2	Time Period-1 At the time of Ambulatory	1000/-
3	Time Period -2	500/-
4	Time Period-1 At the time of Ambulatory and Compensation amount after the completion of study	7550/-
Total		**9550/-**

Note: This is Hindi to English translation of the subsection on compensation amount of a copy of consent form.

Another case is of two women who had participated in the trial by one of the CROs from Ahmedabad. During the second stage of the trial, it was found that they were pregnant and hence could not participate in the study. So the CRO representative discontinued both of them from the study and threatened them to get their pregnancy aborted because child could be born with deformities. These two women had to get it their pregnancies aborted at the CRO itself but when asked about the remaining compensation amount, they were denied it.

> We are helping you to abort the pregnancy for free which itself is a favour we are offering to you. You have not completed the study so we won't give you the remaining compensation amount (Snehal and Pallavi, February 2015).

Therefore in Indian cases, neither do healthy volunteers participate with any altruistic motive nor do the CROs try to develop such motive in the later stages. Participation and adherence of the healthy volunteers is purely based on the financial compensation offered. The threat shows the attitude of CROs because they are not worried about the availability of the volunteers and hence they can bear the cost of the discontinuation of some of the participants. In fact by threatening they want to maintain their authority in power dynamics where volunteers should always be at the negotiating end. When it comes to debating about the motivation based on the financial compensation, the industry uses a series of rhetoric like participation is voluntary but we are paying for the time and travel expenses of the volunteers (Abadie 2010). But in reality, the calculation of the varied compensation offered does not include factors like from where the participant is travelling, how many days he has to stay at the trial site. Instead of that, compensation varies based on the risk involved, blood loss etc. The word used for the participants, '*paid volunteers'* is itself hypocritical. As Abadie said 'How can someone simultaneously be paid to do something and do it voluntarily?' (Abadie 2010: 45).

3.6.3 Source of Information about the Trials

There are different source of information for the first time participants, some of them are advertisement on the websites, social media, word-of-mouth, touts or agents etc. With reference to responses of the participants, it can be said that word-of-mouth and

agents are the primary source of information. Mostly friend's circle and neighbours are the first ones to who give information about such alternate source of income. A friend's circle or peer pressure is the main reason behind influencing the urban unemployed youth who get trapped in the consumerist culture of the urban locality. For women, who are restricted in their houses, neighbours and agents are the main source of information. The CROs use cascading strategy in the hunt of more participants by asking regular participants to spread the word and bring more women and even children, if they require for some specific studies. In exchange of that they get 100 rupees per person for bringing a person for the studies. According to the agent's opinion, these CROs want to prepare more agents to have ample number of participants and to have bargaining power with the agents.

> If we are recruiting volunteers for them, we take two hundred as agent fees. So to save hundred rupees, they will ask volunteers to bring their neighbours, relatives, friends etc. Such is the process... (Anil, February 2015)

Another trend in recruiting more healthy volunteers is through the platform of social media. Though this method is not effectively used in all cases, many research articles are publishing how social media can be used to recruit volunteers effectively. It summarizes that in order to minimize enormous amount of time required for patient recruitment for clinical trials, one need to look beyond traditional recruitment methods, such as print, radio, and principal investigator relationships (Metnick 2015). During the field study, it was found that number of SMSs and WhatsApp messages were posted in bulk to serial participants. The message usually contains phase of the trial, total blood loss, number of in-patient days, number of visits required and compensation amount that would be paid. On one hand, the process of consent taking has become just a formality, by just a mere mention of study objective, compensation granted, and details of study etc. and on the other, through these kinds of informal means, people are encouraged to participate in the research. According to one of the respondents, CROs gather all the data including your phone number which they use later for bulk posting. The irony lies in the process where unemployed youth grappling into consumerist market and buying smart phones out of the compensation amount they receive. The same smart phones are now a very easy source of information to receive recruitment news.

3.6.4 Process of Informed Consent

The current understanding of the conception of the informed consent is influence by the traditional notions of process of consent taking. The process assumes that Principle Investigator (PI) is a humanitarian and objective person while research participants are considered to be always motivated by the altruistic motive. The process purposefully tries to avoid the influence of larger social, economic, political and cultural factors which influence the individual to participate in the trial. The Belmont Report has mentioned about the three major component of the informed consent form: information, comprehension and voluntariness (US Department of Health, Education, and Welfare 1979). Much research has focussed upon the design the consent form in order to make to more comprehensive and informative. In Indian context, the Supreme Court has make mandatory to take Audio-Visual consent in order to take care of the aspects that consent was informed. But in contrast, there is very less literature which addresses the issue of how to determine the participation is truly voluntary (Fisher 2013). Jill Fisher analyzes it in terms of structural coercion and undue influence. She defines the structural coercion and undue influence as:

> Coercion occurs when an overt threat of harm in the structures is intentionally presented by one person to another in order to obtain compliance while Undue influence occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance (Fisher 2013: 357).

The healthy volunteers during an interview shared the process of the informed consent taking. The process emphasizes more on information and comprehension. The volunteers are asked to sit in the lounge where consent form is given to them. Half an hour time is usually given for the detail reading of the consent form and study details. But during this process, none of the CRO staff takes the effort to address the questions of the participants. On the other hand, for serial participants, it occurs like just formality and they just sign the consent form minutes after its distribution. This shows how the process of consent taking has become just formality in clinical trial setup. In India, the structural coercion in the form of oppressive caste, class and gender structures always present the threat to the marginalized poor of the society and it has been already elaborated in the subsection 3.6.1. It is true that staff cannot address these issues at institution level and it requires larger policy level

changes. But at the institution level, the staff can at least take efforts to respond to the needs of healthy volunteers, explain him the risk and benefits underlying each trial ongoing in that research centre. In this way, the decision of a healthy volunteer to participate in the trial will be at least base on information given.

The undue influence also plays a major role in the participation of healthy volunteers. According to information shared by the healthy volunteer, even college students especially from Pharmacy College do come for the trials. Here power dynamics between the research participants and PI plays major role. It might be the case that, students are recruiting themselves because their teacher is involved in that trial and might give him/her good grades for his participation. During the informal interview with CRO data manager, it was revealed that they usually prefer pharmacy students for the trials because they are in need of money for their education as well as know about the trial industry.

3.6.5 Expenditure of the Compensation Amount

The healthy volunteer's expenditure of the earned money through participating in clinical trial is dependent on number of factors like age, gender, socioeconomic position etc. which at times acts separately or all together. In the samples that the researcher has interviewed, all of them spend the money for different purposes like to pay debt, for medical or other emergencies, buying expensive consumer goods, alcohol etc. Shopping of consumer goods such as smart phones, clothes etc. are evident among unmarried youth. It puts them in a vicious cycle of consumerism. For example, one respondent had purchased a smart phone and now he has to spend Rs. 250 every month for the internet pack while his father and mother are daily wagers. But when the healthy volunteers get married, the money is mainly utilized to fulfil the family needs. In maximum number of the cases, respondents have mentioned that they participated in the trials due to financial constraints in the family. In the cases of married women, most common and evident factors were either their husbands were alcoholics, family debt or medical emergencies.

One phenomena which is observable about the healthy volunteers is that initially they started participating in the study because some financial need but even after

satisfying the financial need, they continued their participation. This kind of continuous participation is composite of banalization of risk as well as financial compensation they receive. Healthy volunteers who have the initial fear of participating yet continue the participation until they hear some news of SAEs. In one of the CRO in Mumbai, the trial medicine was injected to twelve young men from Ahmedabad which led to their hands getting swollen. Finally one hand of all the 12 healthy volunteers had to be amputated. The same incidence was shared by an agent whom researcher interviewed in the Ahmedabad and three volunteers from the Mumbai. He said that he got the news from the agent who had sent those 12 men to Mumbai. According to him, compensation of forty thousand was given to each. This news spread like wildfire amongst all the participants through different communication channels which stopped the respondents to continue the participation for some time. A lot of the regular participants had suspended their participation in the clinical trials they were called for. So they classify risky and non-risky CROs based on SAEs news they hear about.

3.6.6 Strategies to Maximize Participation

Phase I trial has minimum 30 days wash out period that means once one trial is completed healthy volunteers cannot participate in the other trial for next 30 days at least (Edelblute and Fisher 2015). But in order to maximize their participation and hence to earn more financial compensation, healthy volunteers use different strategies. In a sample of healthy volunteers researcher had selected, all the participants except two agents were serial participants. Apart from participating in consecutive trials one after the other, they have also participated in two or more trials at a time by using different techniques (See Table 3.2).

Table 3.2

Total Number of Trials and Dual Participation

Case identification	No. Of trials	Two trials at a time simultaneously
Case M1	32	3
Case M2	16	2
Case M3	8	0
Case A1	2	0
Case A2	12	2
Case A3 (agent)	27	3
Case A4 (agent)	14	1

Note: M-Mumbai case, A-Ahmadabad case

It is not like that only volunteers seek to maximize their participation, but also the CROs try to maximize the recruitment, because their profit is always linked to the number of studies they complete and submit the data to the parent pharmaceutical company. That is why initial they used to allow recruitment of volunteers even though the wash out period has not been completed (See Table 3.2). They also allowed the volunteers to participate irrespective of the fact that such volunteer had already undergone another trial. Earlier there was no centralized clinical trial registry to check dual participation due to which the CROs took full advantage and exploited the participants. But today, finally the CROs are mandatory to enter all the details of participants in the registry with valid identity proof. Three volunteers and one agent had mentioned about the online central registry of participants. The researcher could not get hold of further detailed information about this centralized registry. The researcher could not find more details about this registry as to whether it includes names of all participants in India or the state, whether they are owned by pharmaceutical companies or by CROs. According to the information given by an agent, one can still easily invade this system with a number of tricks or strategies. Some of the tricks used by volunteers are producing fake document at the time of

identification, travel to other states for trials, remove syringe remarks through different techniques. In the case of fake documents, women usually produce two identification cards, one with surname before marriage and one after marriage in two different CROs. For men it is acceptable to make a fake identification card and produce this for identification. In fact, CROs encourage these kinds of practices in order to achieve the sample target. There are some typical CROs which do recruit volunteers who are already under another clinical trial. The agent from Ahmadabad has shared information about CROs in Vadodara and in Mumbai which do accept volunteers who are not fit under the inclusion criteria, who are alcoholic or already under trial of other drug. In order to enhance recruitment before wash out period gets completed, some people use ice to rub on their hands to remove syringe marks. This phenomenon of participating in more than one trial at a time can increase the risk of severe adverse event on healthy volunteers. It also raises the question on validity of the data that will be generated. In case of any SAE, it is further difficult for investigators to attribute it to one particular trial medicine. Also if data is not reliable it will have cascading effect on further phases where vulnerability of participants in this phase will increase. Some of the people travel to other states to maximize their participation and agents play a major role in assisting with this. For each volunteer recruited from outside the state, agents get three hundred rupees as extra commission. The agent interviewed was already sending volunteers to cities like Hyderabad and Mumbai from Ahmadabad. Another striking fact came into light was regarding participation of the healthy volunteers in phase II and phase III trials. According to definition, phase II and phase III trials are conducted on the patients of disease which trial medicine proposed to cure. Researcher saw many text message in which it was clearly mentioned that it is a phase II or III trial with amount of blood loss and compensation offered. This is very serious issue because the trials of the patients are done healthy volunteers to achieve the targeted sample size.

3.6.7 Adverse Events and Banalization of the Risk

The institutional banalization of the risk is a peculiar factor in case of professional healthy volunteers. Jill Fisher has discussed the process of banalization of the risk of research staff as well as healthy volunteers (Fisher 2015). This banalization occurs of

both sides i.e. CRO staff and healthy volunteers. The researcher has not interviewed any CRO staff during this study, hence the analysis of the data related to research staff is based on what healthy volunteers have experienced. In case of research staff, there are three ways through which the risk becomes banal for research staff: a perceived homogeneity of studies, Fordist work regimes and data centric discourse. On the other hand in case of healthy volunteers, risk becomes banal through repetitive participation which results in desensitization of risk as well as trust building with researcher staff (Fisher 2015). Overall the routine of the work results in risk becoming banal.

Based on the analysis of the consent form recovered from the healthy volunteers, it is clearly evident that most of the phase I trials have homogeneous research design except some devices where you require special medical procedure (See Figure 3.2). Drug dosing, blood and urine collection, electrocardiogram, physical examination and meals are most of the common activities which are performed in confined setup while conducting phase I trial (Fisher 2015). The important information which needs to be communicated with special emphasis like communicating properties of trial medicine, probable short term and long term side effects and exceptional study demands are ignored due to this perceived homogeneity. The consent form is a mere formal translation of the English to Hindi or any other local language and format of consent form is same for all the trials. This perceived homogeneity convey non-exclusiveness of the studies to healthy volunteers and hence volunteers at a point stops differentiating between studies. As phase I study demands high level of efficiency where each activity has to be conducted according to protocol, the CROs have developed fordist setup to achieve this efficiency. Fordist setup implies mass production of goods and in case of clinical trials mass production of data with typical setup. The figure below shows how protocol dictates activities in a rigid timetable.

Figure 3.2

Fordist Protocol of Phase I trials

Date of study				
Time Period 1	Time Period 2	Time (Hours)	Clock timing	Activity

			(Hours)	
Day 00	Day 00	Minimum 13:00	First 20:00	**Time period 1**: Identification and Verification, Informed Consent method, Alcohol Breath test, Urine test for intoxicant detection, Volunteers accepted or rejected decision. **Time period 2:** Informed Consent method, Tests for inclusion/exclusion and above stated all tests.
		-12:00	21:00	Dinner
		-11:00	22:00	Fasting restrictions, Sleeping alarm
Day 01	Day 01	-2:50	06:30	Daily Morning Activities. After that Cannulation
		-1:00	8:00	Restriction on drinking water. Important tests before taking medicines
		-0:50	8:30	Prescribed Breakfast and sample collection before taking medicine
		0:00	9:00	Study drug given and after that restriction on physical activities
		0:50	9:30	Sample Collection
		1:00	10:00	Sample Collection, Drinking water is allowed
		1:50	10:30	Sample Collection
		2:00	11:00	Sample Collection, Blood sugar test, Other important tests, No restriction on

				physical activity
		2:50	11:30	Sample Collection
		3:00	12:00	Sample Collection
		3:50	12:30	Sample Collection
		4:00	13:00	Sample Collection, Lunch
		4:50	13:30	Sample Collection
		5:00	14:00	Sample Collection, Blood sugar test
		6:00	15:00	Sample Collection, Important tests
		8:00	17:00	Sample Collection, Evening breakfasts
		10:00	19:00	Sample Collection
		12:00	21:00	Sample Collection, Blood sugar test, Dinner
		13:00	22:00	Important tests

Note: This time table is Hindi to English translation protocol subsection of copy of consent form

In order to achieve this, typical setups are organized at the screening and even in wards where healthy volunteers sleep. Even healthy volunteers are not called by their names but by patient identity number. According to Jill Fisher, 'The Fordist organizational processes are intended to facilitate the efficient functioning of the phase I clinic. At the same time, however, they also lend the appearance that these processes are controlling the risk to healthy volunteers' (Fisher 2015: 215).

3.6.8 Perception of Healthy Volunteers of Risk and Mitigation

Healthy volunteers usually make decisions of participating or not for a particular trial based on the risk involved. The measurement of risk is composite of information given by the agent and amount of compensation paid. The agents usually give primary information about the trial molecule like it is composition of already approved medicines so there is no risk. The healthy volunteers measure the risk involved in the trial by comparing amount of compensation given. If the compensation given is very high, they come to a conclusion that the trial is very

risky. So usually they prefer to go for trials which give moderate compensation i.e. 10-15 thousands.

Most of the volunteers had a misconception which is again created by pharmaceutical research knowledge like trial medicine stays in your body for wash out period of one month. Hence to enhance the excretion of the trial medicine from their body they adopt number of measure like drinking lots of water, juice etc. Regarding some trials, healthy volunteers have developed their own knowledge and understanding through experiences, like in cases of psychotropic drugs long term effects are more adverse. One of the healthy volunteers shared an experience of psychotropic drug in which he was suffered from hallucinations for about one month. He said that the hallucinations stopped after he started drinking warm water regularly.

3.7 Summary

The nature of expropriation of healthy volunteers can be divided in three parts: One is the historical socioeconomic exploitation of generations of some class, castes, gender. The historical expropriation includes displacing people out of their land, traditional occupation to make them helpless labour to be exploited. Loss of livelihood in the village, force them to migrate towards the cities.

The other kind of expropriation is experienced by the healthy volunteers but outside the clinical trial setup. The labour when approach to city in search of the livelihood, the already established class exploits the, at minimum wages. Apart from that other institutions like privatization of health care, non-availability of loan and jobs forced them to participate in the clinical trials and exploit their bodies in exchange of money.

The third dimension of the expropriation is the exploitation of the healthy volunteers within clinical trial setup. It is in the form of number of SAEs and commodification of the body. Through clinical trial industry, the starving population is putting its body to work at cellular level to earn money for the livelihood.

Conclusion

Throughout the history, there is a transition in means of expropriation, from the land to surplus labour. It is also clearly coming out of the interviews of the healthy volunteers. Almost all healthy volunteers or their family members belonged to villages with agriculture and allied activities as their source of livelihood. The different social, economic, political and cultural processes alienated them from their land and force them to migrate in the cities in search of livelihood. In cities, they usually become as a major part of unorganized labour whose surplus labour was exploited for the generation of profits out of industrialization. At this juncture in an era of neoliberal revolution, human bodies have been exploited at the micro level as a means of expropriation. It does not mean that previous forms of expropriation do not exist. It is the further expansion of the commercial processes at more micro level to commodify every part of the human body.

Recognizing the fact that clinical trial is most important part of the drug development process which proposes the solutions to human health problems and diseases, the current discourse of the commercialization of the drug development has dehumanized it. Even though pharmaceutical industry called clinical trial participants as a 'Volunteers', it has emerged as a profession in India. The participants recognize themselves as workers of this industry by claiming it a 'part time job' and continuously supply their 'healthy' bodies for experimentation. The serial participation of the healthy volunteers has posed them to serious risks which they are unable to recognize unless there is some Severe Adverse Event (SAE). The perceived risk by healthy volunteers is very much situational and banalised through serial participation. The pharmaceutical protocols also try to divide the SAEs as 'due to clinical trial' and during clinical trial' on the same line and ignores the cumulative impact of the serial participation on human bodies. Unlike the other workers who work in hazardous conditions, healthy volunteers are mobile and hence lack the information of shared experiences of side effects.

Healthy volunteers are usually bound by liberal contracting in a transaction with pharmaceutical industry. The profession of healthy volunteering allows them to participate freely, offer them choices of withdrawal with free mobility during contract period expect for few days when they have to present themselves for the

sample collection. They see it as advantageous by not being like an embodied labour of other professions where physical presence of labour is required. But they certainly ignore the fact that it is a neoliberal imperative to transform the citizen's subjectivities to make feel individuals that they are making their own choices. For example, through a process of informed consent, the healthy volunteers are made responsible for the risk underlie in the research.

There is also a need to recognize the power dynamics between developing and developed world which has forced the migration of clinical research in the developing world. In result, it is using the particular castes, classes and gender in these countries as a 'guinea pig' for the experimentation of the trial medicine. The multinational pharmaceuticals know this fact that it is easy to motivate poor, marginalized unemployed and underemployed working class of these countries by showing prospect of 'easy quick money'. Apart from this fact, they also aware of the fact that in a context of nonresponsive public health services, growing private health services and the doctor-patient power hierarchy in these countries, it is easy to lure the patients to participate in the clinical trials by fluting the rules and regulations.

In solution, India should take some radical steps to free the clinical trials from profit making ventures. It requires many amendments in the existing rules and regulations related to clinical trials. In Indian context, the major amendments in Drug and Cosmetics Act in the year 2005 lead to the over-flooding of the clinical trials of New Chemical Entities (NCEs) in India. This amendment was meant only and exclusively to help foreign drugs companies to reduce cost of clinical trial and use poor, illiterate people of the country as a 'guinea pig'. Apart from that current proposed Drugs and cosmetics (Amendment) Bill 2015, either by default or design, confuses the differences between NCEs and New Drugs in order to allow the trials of NCEs. Therefore it is require to reverse these amendment and brought at par with old Drug and Cosmetics Act. NCEs which get approved as a 'New Drug' in an advanced country should be allowed in India only after complying with rules including conducting pre-approval, mandatory Phase III clinical trials. An independent mechanism for investigation and awarding compensation totally independent from the Investigator and Ethics Committees should be established. CROs who are an agent of pharmaceutical companies should be banned from conducting clinical trials.

Along with this, India also requires to come out of TRIPS agreement and reverse it to patent regimen which will enable the research and production of affordable medicines. It also require to take some radical steps in strengthening public medical education institutions and research institute which will promote the research in line with three parameters prescribed by Supreme Court of India i.e. Risk versus benefit to the patients, Innovation vis-a-vis existing therapeutic options, Unmet medical need in the country.

One thing is now clear that, social, economic, political and cultural factors are very much responsible for the participation in the clinical trials. The primary motive of the healthy volunteers is financial incentive and not altruism. In case of the other phases of the trial, the most of the patients do participate in the trial because of the reasons, such as either their doctors recommended or they do want to access the quality medical care. The power dynamics and information asymmetry plays a major role in the doctor-patient relationship. For that, some doctors may argue that addressing structural issues requires policy level changes and it cannot be addressed at individual level in a clinical setup. It is also said that the doctors are not trained to address these issues. As Paul Farmer et al argues, 'medical professionals are not trained to make structural interventions....Physicians can rightly note that structural interventions are 'not our job' (Farmer et al. cited in Fisher 2013: 367). But the intervention is possible even in the clinical setup and not through radical changes but through small interventions by which doctors can make the participation voluntary and they can also deal with the problem of structural coercion.

In order to deal with problem of structural coercion, researchers can intervene in the process of consent taking itself. As discussed above, due to power dynamics and information asymmetry, the participants usually follow what doctor have recommended for them. So during the process of informed consent, it is the utmost responsibility of the doctors to explore the options available in the standard medical care. He should communicate them the available options including clinical trials along with prospective risks and benefits of participating in the clinical trials. Even if the patient is participating in the trial because of non-affordability of treatment cost, the doctor should tap all the resources to get financial assistance for the patient before encouraging him to participate in the trial.

In case of healthy volunteers, some may think to ban the phase I trials but it will ultimately transfer the burden on the next phases and will become more destructive. On the other hand, ending the financial compensation offered in order to make research participation more altruistic will also slow the process of drug development. Hence ultimately to relay on paid healthy volunteers remains only feasible option. Having said that, the only feasible option will be to rely on paid healthy volunteers, the justice can be done with healthy volunteers by making risk more transparent. The Principle Investigator (PI) can present the number of studies ongoing and risk underlying in each trial to make the decision making more informed. The centralized registry containing participant's detailed information and number as well as nature of trial they have participated can be developed. The data regarding SAEs and deaths related to each trial should be made public. This registry hence will help to enhance the accountability of pharmaceutical industries as well as track the healthy volunteers for long term effects of serial participation on their health.

The researchers can be also be attentive to these structural needs by providing participants more substantive care or health education during clinical studies, post-trial access to care and fair stipends that reflect the burden of time and effort associated with participation. Though Ethics Committees view it as act of undue influence, if we look in to a larger framework of poverty, the failure to compensate individual and inadequate health services are looked as exploitative. Researchers can also learn how to minimize their own biases against disenfranchised groups, especially the poorest of the poor, by recognizing that these problems are not moral or individual failings but structural constraints.

Finally an effective method to address structural coercion would be to confront the material reasons that motivate people to participate in research studies. On the policy level, this translates into advocating for a higher minimum wage, land reforms, universal health care and social security which could significantly mitigate structural coercion.

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