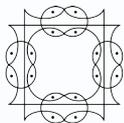


TRIALS AND TRAVAILS

**Perceptions and experiences of
clinical trial participants in India**

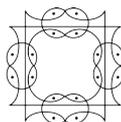


Sama

Resource Group for Women and Health

TRIALS AND TRAVAILS

**Perceptions and experiences of
clinical trial participants in India**



Sama

Resource Group for Women and Health

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All errors and omissions, if and when they occur, are all ours.

Abbreviations

AE	Adverse Events
ADR	Adverse Drug Reactions
AIDS	Acquired Immuno Deficiency Syndrome
BMI	Body Mass Index
BA/BE	Bioavailability & Bioequivalence
BP	Blood Pressure
BPL	Below Poverty Line
CRC	Clinical Research Coordinator
CRO	Contract Research Organisation
CTP	Clinical Trial Participant
CT	Computerised Tomography (Scan)
CTRI	Clinical Trial Registry of India
CoI	Conflict of Interest
CVD	Cardio-Vascular Disease
CPD	Chronic Obstructive Pulmonary Disease
CDSCO	Central Drugs Standard Control Organisation
CIOMS	Council for International Organisations of Medical Sciences
DCA	Drugs and Cosmetics Act
DoH	Declaration of Helsinki
DTAB	Drugs Technical Advisory Board
DCGI	Drugs Controller General of India
EC	Ethics Committee
ECG	Electrocardiogram (Test)
FDC	Fixed Dose Combination
GSR	General Statutory Rules
G6PD	Glucose-6-Phosphate Dehydrogenase Deficiency
GCP	Good Clinical Practices
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
ICMR	Indian Council of Medical Research
IP	Intellectual Property

ICF	Informed Consent Form
IPD	Indoor Patient Department
IPAB	Intellectual Property Appellate Board
IC	Informed Consent
INR	International Normalised Ratio
IEC	Independent/Institutional Ethics Committee
IRB	Institutional Review Board
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MCI	Medical Council of India
MHRA	Medicines and Healthcare Products Regulatory Agency
MoHFW	Ministry of Health and Family Welfare
NACO	National AIDS Control Organisation
NCEs	New Chemical Entities
NMEs	New Molecular Entities
NGO	Non-Governmental Organisation
NRI	Non Resident Indians
NBEs	New Biological Entities
OPD	Outdoor Patient Department
PLHIV	People Living with HIV
PTA	Post Trial Access
PwC	PricewaterhouseCoopers
PATH	Program for Appropriate Technology in Health
PMS	Post Marketing Surveillance
PIL	Public Interest Litigation
R&D	Research and Development
RTI	Right to Information
SMO	Site Management Organisation
SOP	Standard Operating Procedures
SAE	Serious Adverse Events
TRIPS	Trade Related Aspects of Intellectual Property Rights
UNESCO	United Nations Educational, Scientific, and Cultural Organisation
USFDA	United States Food & Drug Administration

WTO	World Trade Organisation
WMA	World Medical Association
WHO	World Health Organisation

Introduction

The search for new medicines and drugs, and the need to improve existing treatments and cures, is part of the long history of medical sciences. Medical sciences, along with technological advances in other sciences, are constantly exploring newer and better treatments, diagnostics, and preventive measures for age-old diseases, as well as for newly emerging medical challenges hitherto unknown in human history. These challenges are compounded further by sharply rising inequities in health expenditure, disparities in health care and access to health care facilities, as well as the varying degrees of access to other socio-economic determinants. The advancement of the medical sciences is crucially based on clinical research, and clinical trials are considered to be “the most definitive tool for [the] evaluation of the applicability of the clinical research”.¹

A clinical trial is defined (Friedman, L. et al 2010) as ‘a prospective study comparing the effect and value of intervention(s) against a control in human beings.’² A clinical trial must employ one or more intervention techniques. These may be a single or a combination of diagnostic, preventive, or therapeutic drugs, biologics, devices, regimens, or procedures.³ Clinical trials result in the discovery of newer medicines for diseases or in the improvement of existing regimens.

Unfortunately, the history of this fundamentally important process is marred by episodes of gross violations of human rights, the most notorious of which eventually led to a judicial process - the Nuremberg Trials (1945-1949), to bring to justice those involved in war crimes during the Second World War. However, at the time, there was no law to guide the proceedings, a fact that was used as a prime defence by those accused. From the judgement handed down in this trial emerged the 10-point Nuremberg Code.⁴ Following the Nuremberg Code, the Helsinki Declaration of World Medical Association (WMA) in 1964 was another important document adopted by the world community. It continues to be, even today, after many rounds of revisions, a guiding source for the regulation of clinical trials. Since 1964, the Declaration has undergone six revisions, with the latest revision in 2013.

The Helsinki Declaration includes principles relating to the obligations of physicians with regard to informed consent and transparency in the conduct of research involving humans, including clinical trials. The Declaration was a landmark in the recognition of the rights of vulnerable groups.⁵ In 1980, the Indian Council of Medical Research (ICMR) published its own Policy Statements on Ethical Considerations Involved in Research on Human Subjects for the conduct of clinical research in India. The first formal guidelines were published in 2000 and then revised in 2006 entitled Ethical Guidelines for Biomedical Research on Human Subjects.⁶

The Council for International Organisations of Medical Sciences (CIOMS), established jointly by the World Health Organisation (WHO) and the United Nations Educational, Scientific, and Cultural Organisation (UNESCO), began its work on ethics in biomedical research in the late 1970s. The CIOMS guidelines were developed in cooperation with the WHO: *to indicate how the ethical principles that should guide the conduct of biomedical research involving human subjects, as set forth in the Declaration of Helsinki, could be effectively applied, particularly in developing countries, given their socioeconomic circumstances, laws and regulations, and [their] executive and administrative arrangements.*

After the publication of the Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects in 1982, there have been a number of revisions of these guidelines, with the last revision being made in 2002. Although neither the Nuremberg Code nor the Helsinki Declaration are legally binding documents, they have nevertheless provided direction and have been taken into consideration in the framing of national laws on the regulation of clinical trials on humans in different countries.⁸

While the ethical guidelines and regulatory frameworks for the conduct of clinical trials were being evolved, the underlying economic forces, which were driving the growth of the clinical trials industry, could not be ignored. The priorities for clinical research began to be increasingly defined by the profit motive in developing and marketing drugs faster. These priorities are neither fixed nor clearly defined,⁹ as different countries have different needs, priorities, capabilities, and resources for dealing with this constant search for newer and more effective medicines. Under the pressure of economic forces, clinical trials, hitherto acknowledged as innovative

attempts to alleviate human sufferings, turned into commercial ventures, with the goal of profit maximisation driving the process. Hence, it is no wonder that drugs that are profitable are the ones that are discovered and marketed.

This situation is compounded by the overall situation of the drug market. As per the 2010 report by the consultancy firm PricewaterhouseCoopers (PWC), the main markets for the drug industry, namely Europe, Japan, and North America, were recording sluggish growth at 5.8 per cent, 2.1 per cent, and 1.4 per cent respectively.¹⁰ The report further stated that impending policy changes promoting the use of generics in these markets were expected to dent the top and bottom lines of the global pharma majors. It is important to note here that the promotion of generics in the developed countries is one of the factors pushing the pharma multinationals to enter the markets in the developing world. In the United States, the ratio of the sale of prescription drugs to generic drugs has more than reversed from 53:47 in 2003 to 22:78 in 2010.¹¹ The goal of these companies is to promote their prescription drugs in the developing world. The PWC report of 2010 further stated that the industry is looking for newer ways to drive growth owing to the situation in the top drug markets of the world. One of these newer ways of driving growth was to explore opportunities in developing countries and in their emerging markets. These developing countries had reached a certain level of human resources and now also possessed the requisite medical expertise and infrastructure that could be used for conducting clinical trials. Further, these countries offered a distinct cost advantage owing primarily to their much cheaper human resources.¹²

Finally, the developing countries also largely do not have well-defined regulatory frameworks, the absence of which makes it easier to conduct clinical trials with tokenistic approvals, and sometimes even without them, thereby providing a time and cost advantage to the international pharma majors. As can be seen from the above-mentioned PWC report,¹³ the industry is sensitive to policy changes in the target countries. When the policies are not favourable, the industry starts exploring opportunities in those countries where the regulations are more favourable. In the absence of clearly defined regulatory structures in the developing world, the regulations in the developing countries are made, amended, or adapted to suit the needs of the multinationals in the name of growth, research, and development.¹⁴

These strategies are employed in order to maximise profits. One of the factors for the desperation to achieve profit maximisation is the expiry of a patent in 20 years. This period of 20 years also includes the period for conducting clinical trials after discovery and for registering the patent for the new molecule. Hence, once the molecule is discovered, there is considerable pressure and anxiety to bring the drug to the market as quickly as possible, so as to recover the costs incurred on research and to achieve desired profits. Clinical trials conducted in developing countries in the context of weak regulatory oversight, facilitate the sidelining of many of the protocols designed to protect human participants in clinical trials.¹⁵

It is frequently argued that the rush to maximise profits is justified because of the huge investments required for the discovery of new molecules and because the time to achieve this is limited in a Patent-dominated scenario. There are various estimates about the costs required for discovering a new molecule. It is stated to be over \$ 1 billion in the United States and Europe.¹⁶ However, some scholars argue that this claim needs closer examination. Bajpai¹⁷ (2013) quotes a more realistic estimate by a consumer advocacy group, *Public Watch*, which is \$ 100 million, one tenth of the figure claimed by the industry.

It is a well-known fact that profit maximisation also drives pharma multinationals in the developing countries. However, problems start arising when the ethics of clinical research are violated for the sake of profit maximisation and when the rights of clinical trial participants are infringed.

1.1. Clinical trials in the Indian context

Schedule Y was inserted in the Drugs and Cosmetics Rules in 1988. Schedule Y specified the phase lag for clinical trials. This meant that if a Phase III trial had been conducted outside India for a particular drug, it was mandatory to conduct a Phase II trial in India before a Phase III trial.¹⁸ In 2005, the Government of India made the country fully compliant with the Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement of 1994, and thereafter changed its rules in favour of pharmaceutical companies to promote new clinical trials in India. The provision of phase lag in Schedule Y (1988) was removed in the amendment of 2005.¹⁹

The government opened up India to concomitant Phase II and Phase III trials of new chemical entities (NCEs) discovered abroad as part of a larger slew of amendments in its Drugs and Cosmetics Act, 1940, and Rules, 1945, to “facilitate” global clinical trials in India. It was felt that this kind of “liberalisation” would place India on the global clinical trials map. Simultaneously, in the period following the 2005 amendments, there were attempts by the industry as well as the government to attract clinical trials to India. Owing to these favourable changes, very ambitious estimates were made about the prospects of the Indian clinical trial industry. Devarakonda (2013)²⁰ quotes a study by Frost and Sullivan that estimated that the USD 500 million business in India would reach USD 1 billion by 2016. The literature on the clinical trial industry in India describes the country as an attractive site for conducting clinical research,²¹ is unanimous for the following reasons:

- Large pool of treatment-naïve²² patients^{23,24}
- Large number of qualified medical professionals^{25,26}
- Distinct cost advantages^{27,28}

The Report of the High Level Group on Services Sector (2008)²⁹ of the Planning Commission of India described clinical research as a very promising area. It noted that many multinational companies had started working in India and were conducting research through contract research organisations (CROs). The report also emphasises the following factors as the fundamental strengths of India, which include a diverse gene pool, a large patient pool with diseases such as heart diseases, diabetes, and psychiatric disorders prevalent in industrialised countries, a treatment-naïve population, competent medical professionals, good hospitals, and potential cost and time savings.

India offers substantial advantages in terms of cost efficiency. The cost of conducting a trial in India is lower by 50 per cent than the cost in the United States.³⁰ It is apparent that the Report of the High Level Group tries to attract pharma multinationals to India with claims about Indian patients possessing the relevant disease profiles that are alleged to have relevance to people living in the “developed” world, and does not mention India’s own priorities of treating communicable diseases such as malaria and tuberculosis. The report states that cheap human resources as a

contributing factor in cost saving, differences in costs associated with patients is another cost-saving factor. The report refers to the widely shared assessment that:

The regulatory structure in India on all aspects of the drug industry including the clinical trials is weak and not equal to the challenges posed by technological development.

However, the recent past has witnessed a decline in the Indian clinical trial industry.³¹ The conduct of clinical trials in India raises various issues regarding the unethical conduct of these trials and has led to the demand for greater protection for participants as well as for strict regulatory provisions to govern the ethical and proper conduct of clinical trials in the country.

The comments from industry representatives that ‘the clinical trial industry in India is in shutdown mode’, the scaling back of the operations of multinationals, and the ‘pausing of patient enrolment’ indicate a reversal to some extent in the trend of perceiving India as a favoured destination.³² The overall numbers of new applications and approvals for existing applications for clinical trials have been declining. This is evident from the decision of the Drug Controller General of India (DCGI) to clear only 12 trials for 2013 (till April), as compared with 325 in 2011 and 2,262 in 2012.³³

Public outcry and litigation have visibilised the violation of rights of participants as well as the gaps in regulation, leading to the drop in the number of clinical trials in 2013.

1.2. Regulatory environment

The conduct of clinical trials in India is regulated and governed by ‘Ethical Guidelines for Biomedical Research on Human Participants’ (ICMR, 2006), Schedule Y of the Drugs and Cosmetics Act, 1940, and the Indian Good Clinical Practices (GCP). However, the ICMR guidelines are not legally binding. Both the ICMR guidelines and Schedule Y do not include provisions with regard to penalties for violation of the guidelines and rules, and are also silent on the regulation of CROs. Efforts to make the entire process more transparent and accountable are also missing from the existing framework. Owing to these loose ends in the current framework, there have been

many instances of violation of the principles and norms governing the conduct of clinical trials, as well as the functioning of regulatory authorities. The two reports that bring this out clearly are the 59th Parliamentary Standing Committee Report on the functioning of the Central Drugs Standard Control Organisation (CDSCO) (May 2012)³⁴ and the 72nd Parliamentary Standing Committee Report on the alleged irregularities in the conduct of studies using the Human Papilloma Virus (HPV) vaccine (August 2013).³⁵ Following these disclosures, a few changes were made in the regulatory framework, which include the formulation of guidelines for the compulsory registration of ethics committees and guidelines for awarding compensation for adverse events (AEs). In 2013, the Ministry of Health and Family Welfare (MoHFW) made audio-visual recording of the informed consent process for all participants in clinical trials compulsory and in addition to written consent.³⁶

1.3. Rationale for the study

The history of clinical trials in India has not been very different from the history of clinical trials globally. There have been many instances of unethical clinical trials conducted by government bodies, pharma companies and medical institutions/hospitals resulting in serious violations of the rights of clinical trial participants. In 1983-84, ICMR initiated a Phase IV (Programme Introduction) trial in urban and rural centres to assess the acceptability of Net En contraceptive in order to introduce injectable contraceptives in the National Family Welfare Programme.³⁷ A rural health centre in Patancheru, a village close to Hyderabad in Andhra Pradesh, was one of the centers where this study was conducted. A “camp” was organised in Patancheru to introduce the injectable and paramedics were given the task of recruiting twenty women from the poorest class for the trial.³⁸ Investigations by women’s rights groups revealed that the process of taking informed consent was not done properly and that the clinical trial participants were not made aware about the possible side-effects and contraindications of the drug being tested. The argument given for such unethical action was that if they had been informed about the experimental stage and possible side-effects of the injectable, no one would have volunteered.

The Institute of Cytology and Preventive Oncology (ICPO), an institute funded by the ICMR, between 1976 and 1988, carried out a study to identify relevant risk

factors and the detection and management of the precancerous and early cancerous lesions of the cervix in order to prevent invasive cancer of the cervix. The ICPO team selected approximately 1158 women with varying degrees of cervical dysplasia for long term follow up. A few years after the conclusion of this project, it was revealed that the study had been conducted unethically. In spite of the early detection of the lesions during the study period, women were not offered immediate treatment for cancer. Some women developed cancer and died before the end of the study. The ICMR-ICPO cancer study is an important reminder of the many ethical issues in clinical trials, including the protection of participant rights, the standard of clinical care provided during a trial, and relevant public health dimensions and implications of a research.³⁹

At Maharaja Yashwantrao (MY) Hospital, Indore, 73 clinical trials were conducted between 2008 and 2010 in which 81 persons suffered serious adverse events leading to deaths including 18 children. These were not reported and no compensation was given in these cases. The Economic Offence Wing (EOW) of the Madhya Pradesh Government presented its report in June 2011 highlighting many occurrences of ethics violations during the trials in Indore. The report pointed out that the core principles of the informed consent were disregarded during the trials as well as many instances of clear conflicts of interest. The Swasthya Adhikar Manch and others from Madhya Pradesh have centre-staged the ethical violations in the conduct of the clinical trials. A PIL was filed in January 2012 in the Supreme Court highlighting these violations and concerns regarding global clinical trials.

Another noteworthy example is that of the clinical trials conducted on the survivors of the Bhopal gas tragedy at the Bhopal Memorial Hospital and Research Center (BMHRC) which was set up in year 2000 as per the order of the Supreme Court of India to provide health services to the gas victims. From 2005–2008, the BMHRC was engaged in 10 different trials involving pharmaceutical companies such as Pfizer, Sanofi, Astra Zeneca, etc. An RTI inquiry revealed that 80 per cent of the trial participants were victims of the gas tragedy. In most cases, it was found that information about the clinical trial was not provided to the participants. The consent forms were signed by either the principal investigator (PI) or the CRO representative.

Many clinical trial participants have neither been paid compensation nor have they been provided with travel and meal reimbursements as mentioned in the protocol.⁴⁰

Another notable example of the violation of ethics in clinical trials was the Human Papilloma Virus (HPV) Vaccines demonstration project in 2009 conducted on 23000 girls in the age group of 10-14 years. These projects were conducted by Program for Appropriate Technology in Health (PATH), a US based NGO in collaboration with the Andhra Pradesh and Gujarat state governments, and technical support provided by the ICMR. The funding to PATH was from Bill and Melinda Gates Foundation (BMGF), with the vaccines provided free of cost by the manufacturing companies Merck Sharp Dohme and GlaxoSmithKline for these “projects”. The fact-finding report by Sama⁴¹ of the HPV clinical trial in Andhra Pradesh, along with other similar efforts by health groups, women’s groups, as well as the fact of the matter being raised in Parliament, exposed the many serious lapses in the conduct of the HPV clinical trials. Eventually in 2010, the trials were suspended.

Thus, the mere formulation of regulatory provisions, or the imposition of restrictions on clinical trials conducted by private companies and institutions, or the attempt to ensure that most clinical trials are conducted in public-funded institutions may not guarantee the rights of clinical trial participants. As is evident from the previous sections, the government as well as non-governmental entities, private institutions, and companies have all been complicit in the unethical conduct of clinical trials in India.

1.4. Sama’s work on clinical trials

Sama’s work in the context of medical research in India began with its engagement in the campaign against unethically tested and invasive hormonal contraceptives, and the anti- fertility vaccine. Sama members were also involved in the campaign against the violation of the rights of women participants in the ICPO-ICMR study on the progression of cervical cancer that came to light in the mid 90s.

As mentioned above, in March 2010, members of Sama took the initiative to conduct an investigation of the HPV vaccine study in Andhra Pradesh. The Sama investigation

contributed to the setting up of a government appointed inquiry committee that confirmed their findings. In April 2010, the Ministry of Health suspended the study.

In 2011, Sama co-organised a National Consultation on Regulation of Drug Trials in New Delhi. The consultation was attended by nearly 60 participants, who mainly comprised of representatives from activist health networks, the medical and scientific community, media, legal experts, women's groups and policy makers. Both the broader context of clinical trials as well as specific case studies of clinical trial malpractice were discussed. The consultation resulted in a set of specific recommendations regarding the ethics and governance of clinical trials.

In 2012, Sama conducted an exploratory study on clinical trials by Swiss pharmaceutical companies in India along with the Berne Declaration based in Geneva. The aim of the study was to verify relevant ethical standards followed by Swiss Companies in India.

In 2013, Sama along with LOCOST, Drug Action Forum-Karnataka, and Delhi Science Forum filed a PIL in the Supreme Court. The PIL highlights the serious failures to comply with legal and ethical requirements vis-a-vis informed consent, adverse events and ensure medical management of short and long term injuries of participants. The failure of the Ethics Committees in protecting the rights of clinical trial participants by allowing the trial to be conducted in young girls from socio-economically backward families and where medical facilities were poor or non-existent, are also raised by the petitioners.

On 11 November 2013, the Hon'ble Chief Justice P. Sathasivam and Justice Ranjan Gogoi of the Supreme Court issued notice to all the respondents, which includes, PATH, ICMR, the Union Ministry of Health, State governments of Andhra Pradesh and Gujarat and the Ethics Committees of the demonstration projects.

A submission was made by Sama and LOCOST to the MoHFW in response to the Supreme Court Order, which had invited submissions from organisations with regard to monitoring and regulation of clinical trials.

Conclusion

These engagements and experiences with regard to the conduct of clinical trials foregrounded extremely critical areas for continued inquiry and advocacy in India. In particular, the significant gap in the advocacy and research for the health and rights of clinical trial participants, who are the fulcrum of clinical trials, compelled urgent attention.

Methods

We employed qualitative exploratory methods to meet the study objectives. Our choice of qualitative methods was driven by three factors. Firstly, to the best of our knowledge, there is very little empirical research available in India on clinical trials from the perspective of clinical trial participants. Secondly, drawing upon our knowledge and understanding of the terrain of clinical trials in India, we conjectured that the field setting would pose a challenge in employing a quantitative approach to the research questions being explored. Finally, due to scarce literature on the topic of enquiry in India, employing qualitative methods, we considered, would help us get deeper insights into the various aspects and set the stage for further work.

This chapter is organised in nine sub sections - namely, study objectives and research questions, study sites, sampling, data collection, ethics review process, sampling techniques, criteria and selection of study sites and key informants, data analysis and challenges during research or limitations encountered during the conduct of the research.

2.1. Study objectives and research questions

The following specific objectives of research were drawn up to explore the perspectives of the clinical trial participants:

- a. To ascertain the motivations of clinical trial participants (CTPs)⁴² behind their decision to participate in clinical trials.
- b. To explore the perceptions of CTPs and their understanding of the different concepts and processes associated with clinical trials.
- c. To explore in-depth the perceptions and understanding of other key actors relating to clinical trials such as Principal Investigators (PIs), representatives of Contract Research Organisations (CROs), Clinical Research Coordinators (CRCs), representative of pharmaceutical company (SP), Programme Managers (PM) and members of Ethics Committee (EC) regarding the processes involved

in designing and conducting clinical trials, as well as their attitudes towards CTPs.

The research questions that guided the exploration included:

- a. What is the overall profile of CTPs?
- b. What factors influence or contribute to CTPs' decisions to participate in a clinical trial?
- c. What are the networks and processes involved in the recruitment of CTPs in India? How do all the key actors, including the CTPs perceive the different concepts and processes related to clinical trials including informed consent, compensation, insurance, post-trial access to treatment in case of adverse events?
- d. What is the understanding of key actors about the ethical, legal and commercial aspects of clinical trials?
- e. What is the level of understanding of key actors, especially PIs, about the new developments in the field of clinical trial regulation in India?

2.2. Study sites

2.2.1. Selection of states and cities

The study was conducted across 37 institutions located in seven cities from four states of India.

The four states were: Andhra Pradesh (Southern India), Gujarat and Maharashtra (Western India), and Delhi (Northern India). The selection of the states was guided by the information available in the Clinical Trial Registry of India (CTRI) and the understanding of the broader context of political economy of clinical trials industry in India and its overall structure and organisation particularly in these four states. More specifically, two criteria were jointly employed for selection of the states and cities drawing upon the data from the CTRI, which provided insights into the distribution of trial sites and types of trials across states and cities – the number of trials conducted in the city as per the CTRI in year 2011, and the stages relating development of clinical industry in these states and cities. In 2011, we found that 3,754 trials were registered in CTRI. The data indicated that a larger number of trials are taking place

in the aforementioned states in the country. While the clinical trial industry is quite substantial in Maharashtra, Delhi and Gujarat, it is growing rapidly in Andhra Pradesh. We chose these states for pragmatic reasons of field work to best answer the objectives in the limited time of the project.

The study team selected the specific cities in these States based on the actual numbers of trials being carried out in those cities. However, special attention was given to small cities/towns with fewer number of clinical trials to ensure heterogeneity in the sample.

2.2. Selection of institutions

An extensive search was conducted through the CTTRI. This search provided data on hospitals (both private and public), medical colleges, nursing homes, clinics, research institutes and CROs that were conducting clinical trials across the country. This provided us insights into the overall profile of the clinical trial industry across states.

2.3. Sampling

2.3.1. Sample size, constituencies and sampling methods

We aspired to include at least about 40-50 institutions and about 40-60 individual clinical trial participants. The actual sample was determined by saturation of the responses when it was felt that the information collected was getting repeated. The actual sample size was determined by the permissions granted by institutions to interview the KIs as well as the CTPs during the project period. We were able to include 37 institutions and interviewed 31 KIs and 36 participants.

While majority of the KIs in this research were PIs, we also interviewed the CRCs, PM, CRO representatives, pharma company representative, EC members and collected information on different aspects related to the conduct of the clinical trial for triangulation of the data.

We relied on the purposive sampling, given the field setting as well as the qualitative methods approach to explore research questions that we set out with.

2.3.2. Inclusion criteria for CTPs

Inclusion of CTPs in the study was determined by:

- (i) if the CTPs were either currently participating in a clinical trial or had participated during the past year; and
- (ii) if the CTPs were willing to be a part of the study.

2.4. Data collection

2.4.1. Tools of data collection

The study entailed in-depth interviews with KIs and CTPs. We developed initial topic guides specific to study participants' categories drawing upon the research questions. The topic guides evolved through by the concurrent data collection to ensure that the emerging themes relating to the research questions were pursued during the data collection and saturation of emerging relevant themes was achieved.

2.4.2. Data collection and documentation

All participants took part in at least one semi-structured in-depth individual interview. Depending upon the type of consent obtained, in-depth interviews were either audio-recorded using digital recording device or were documented using traditional method of field notes, which were then expanded eliciting details of the interviews along with field observations by the respective field researchers/investigators. Audio interviews were transcribed and translated in English. Transcriptions were complemented with field notes. In case of any gaps or missing data, we approached the respondents seeking clarifications to fill in these gaps as much as possible. To maintain privacy of the study participants, all the identifiers were removed and the data was anonymised. The names of participants, institutions and places that could potentially breach privacy, were removed from the data.

Group discussions were conducted to gather the perceptions regarding participation in clinical trials. We prepared a topic guide to facilitate group discussions.

To ensure confidentiality of data, the data was only accessible to the research team. The digital copies of the data were stored in password protected systems. The print/hard copies of the data and original field notes were stored in locked cabinets.

2.5. Data analysis

Narratives were analysed by using a thematic analysis approach. The translated interviews were coded and the codes were grouped into homogeneous themes. These themes were organised as per the various components of the clinical trial process such as recruitment, informed consent, etc. Perspectives of both CTPs and KIs were collated under these broad themes which are presented as chapters in the report. A comprehensive understanding of these themes reflecting on the objectives of the study was weaved together from the chapters and is presented in the concluding chapter.

2.6. Conduct of the study and research processes

2.6.1. Study period

The study commenced in April 2012. The data collection at various sites across the four states – Andhra Pradesh, Gujarat, Maharashtra, and Delhi - was conducted from May 2012 to March 2013. Analysis and report writing was completed by December 2013.

2.6.2. Literature review

Review of literature, was carried out to understand the philosophical, ethical, theoretical and empirical dilemmas surrounding clinical trials. The insights from the literature review also informed the formulation of the topic guides, i.e., the data collection tools for various constituencies.

2.6.3. Constituting and training research team

The research team consisted of the central team and four other field/regional sub-teams. The field setting required us to set up such a research team. The primary team located in New Delhi was involved in all stages of the project conceptualisation,

development, implementation and report writing. It consisted of five members, two of these members have been engaged over the past five years in Sama's research on ethical issues of clinical trials and advocacy aimed at improving overall conduct of clinical trials in India, and required compliance with relevant ethical guidelines and regulatory instruments. They were also involved in a fact-finding mission to investigate clinical trial violations, and developing a detailed critique of the guidelines for compensation during clinical trials.

As the data was to be collected from multiple sites spread over four states, it was necessary to constitute local teams. This enabled us to have sub-teams at study sites equipped with adequate competencies in local languages in the four states - Maharashtra (Marathi), Gujarat (Gujarati), Andhra Pradesh (Telugu) and Delhi (Hindi), familiarity with the local contexts, familiarity with the geographical area and the socio-cultural practices. Sub-teams also made identifying respondents for this research project, especially participants, efficient.

The entire project team underwent an in-house orientation facilitated by Sama team members with the required training and experience in empirical research and by those who have been involved in work related to clinical trials in India. This was aimed at developing a shared perspective on the broader context of clinical trials in India making the entire project team well versed with the overall study, its goals and rationale. The team members, particularly the local investigators, were also given orientation and training in research ethics obligations that the team was expected to comply with. This training also included discussion on field setting, likely challenges it might pose and the possible ways to address them. This was a collective on-going process.

2.6.4. Access to institutions, participants and key informants

Two methods were employed to approach participants as well as key informants - one was through institutions and the other through communities. We contacted 122 institutions from both the private/corporate and public health sectors in the selected cities across the four states.

Table 2.6.4.a

Research site	Number of institutions approached
Ahmedabad	30
Vadodara	3
Mumbai	16
Pune	20
Nagpur	10
Hyderabad	15
Delhi	28
Total	122

Table 2.6.4.b

Research Sites/Cities	PIs	CRC	CROs	Sponsor	PM	EC	Total
Ahmedabad	3	2			1		6
Vadodara	1	1					2
Mumbai	3	1	1				5
Pune	1						1
Nagpur	1					1	2
Hyderabad	5	2					7
Delhi	3	2	2			1	8
Total	17	7	3	1	1	2	31

Thirty seven institutions permitted us to interact with either CTPs and/or PIs/CRCs. Of these, only seven institutions - Gujarat-2, Andhra Pradesh-2, and Maharashtra-3 - allowed access to participants. Wherever permission was given, the research team conducted interviews with Deans/Heads of Departments of Hospitals, PIs, CRCs, and members of Ethics Committees. Permission was further sought from them to interview participants.

Table 2.6.4.c

State	Men	Women	Total
Gujarat	16	4	20
Maharashtra	5	4	9
Andhra Pradesh	1	5	6
Delhi	1	-	1
Total	23	13	36

The consent process with prospective individual study participants was multi-layered, which is described later in the sub-section “seeking informed consent”.

The second way of approaching CTPs was through communities. At certain sites, we organised discussions with communities. These were facilitated by the local community based groups, non-governmental organisations or patients’ groups. After discussions with the communities, some of the participants in the discussion came back to the research team and were willing to participate in the study and share their experiences as CTPs. We could include four CTPs from this process - one from Delhi and three from Maharashtra.

2.6.5. Conduct of group discussions

The discussions were held through community based organisations in the areas, and also through patients groups. The discussions were held in school playgrounds, training spaces of the local organisations that assisted us in conducting the discussions. We could conduct group discussions at two sites in Gujarat, three in Maharashtra and two in Delhi.

2.7. Ethics Review

The project proposal was reviewed by the Ethics Committee of Sama.⁴³ Some of the key aspects of research ethics obligations were discussed during the review by the EC and are briefly presented here.

2.8. Meeting research ethics obligations

2.8.1. Seeking informed consent

We complied with the standard prescribed process for seeking informed consent of the prospective participants in the study. As mentioned earlier, it was a multi-layered process. First, we approached the aforesaid short listed institution and explored with the respective PIs for their interest in participating in the study. Some of the PIs agreed to participate without requiring us to go through processes seeking additional permissions. However, often, particularly in the public health institutions, PIs asked us to seek required permission from their Dean, the Head of the Department or from the EC. In one hospital, access was denied by the EC even after protocols were presented by the research team.

Once we reached the prospective individual study participants, we followed the norms of seeking consent. Prior to the interview, the researchers provided the prospective participants – KIs and CTPs - information about the study, the mechanism to ensure their privacy, confidentiality of the data collected, anonymising the data, reporting of only aggregated data as opposed to individual level data, potential future use of the collected data, and the estimated time for completing the interview. They were also informed about their right to decline to participate, right to withdraw at any point during the interview or not to respond to certain questions if they so desired. We also informed them our need for audio recording the interviews in the interest of efficiency and quality of data if they consented for the same. Their consent for audio recording was recorded explicitly in the consent form. In case of those who declined audio recording of their interviews, we relied on our field notes, which were then expanded.

In the process of seeking consent, the field investigators encouraged the prospective study participants to seek clarifications, if necessary. This was aimed at facilitating respondents' decision making regarding their participation in the study in as informed and voluntary a manner as possible in the given field setting. Care was taken to ensure that the respondents, particularly the CTPs were comfortable with their decision to participate in this research - participants were provided sufficient space and time during the process of consent to read the study information sheet and the consent form and seek clarifications.

All clinical trial participants and key informants who had consented were provided with signed copies of the study information sheet and the consent form. The consent form was developed in English, Hindi as well as in other languages such as Telugu, Urdu, Gujarati, and Marathi, as deemed appropriate for the study. Verbal permissions were taken from the participants who were part of the community based group discussions.

2.8.2. Sites of interviews and privacy

The study participants were encouraged to choose the preferred interviews sites, which were mostly their residences or their work places, particularly for KIs. This was both to respect their choices and also to maintain as much privacy as possible during the interviews.

2.8.3. Compensation for study participation

Since most of the interviews were held at the residence or work places of participants, no travel expenses were paid.

2.8.4. Maintaining confidentiality

The confidentiality of study participants was maintained throughout the research study. Anonymity was ensured by maintaining codes in the process of data entry, data analysis, and data presentation. Only the research team members had access to the data collected, which has been stored at a secure location in Sama.

2.9. Limitations

In the course of the conduct of this research, the team encountered several challenges. We briefly describe them and their implications for the study and study findings below:

- a. We had to often route our search for PIs and CTPs through institutions which serve as clinical trial sites. Several institutions refused to grant us permission to meet with clinical trial participants or PIs. At times they simply appeared evasive with no explanation provided for refusal of permission.

- b. As a result, access to participants turned out to be an extremely challenging task, far more difficult than what we had anticipated at the outset. We are likely to have lost out on some of the most critical perspectives of the CTPs. It is possible that by not being able to include participants from some of these institutions, we missed out on capturing experiences of CTPs, which could have been indicative of violations of their rights as CTPs.
- c. The field setting and the manner in which the clinical trial industry is organised, the consent seeking process was often layered involving multiple stages. This implied, when permitted by the gate keepers, that our access to prospective study participants, particularly CTPs, was not only restricted but was influenced by the bias of the institution heads or other gate keepers at these establishments, including PIs. This might have affected the study sample of individuals and again, we might have missed out on some critical perspectives of individual study participants, particularly CTPs.
- d. We also had to forego some institutions either because their own ECs did not permit us to include their institutions in our study or the EC processes were delayed to the extent that it could not befit the time frame of the present study.

Profile

This chapter presents the profiles of the 36 Clinical Trial Participants (CTPs) and also provides the overall profile of participants as perceived by the Key Informants (KIs) involved in the conduct of clinical trials.

3.1. Profiles based on interviews with clinical trial participants

The background of the CTPs with respect to their gender, age, education, work/occupation, income and assets, caste and religion, marital status, family type, location, etc., is presented here. Of the 36 participants interviewed, 23 were men and 13 were women. Two of these women were not participants themselves but were interviewed as parents of children recruited for a vaccine trial. Although a little more than half of the sample comprised of women, this cannot be extrapolated to the larger, general CTPs. It is not sufficiently clear as to whether gender in any way impacts participation in clinical trials or if gender as a criteria for selection is used by those who conduct clinical trials.

3.1.1. Disease profile

Most of the CTPs were experiencing a range of health issues in the course of the treatment, during which, they were approached to participate in the clinical trials. Only three women CTPs were approached to participate in the trials for cervical cancer screening, given their possible vulnerability as sex workers to Human Papilloma Virus (HPV) infections. Participants were recruited in clinical trials for health problems such as hypertension, cardiac problems, obesity, chronic obstructive pulmonary disease (COPD), gastritis, diabetes, influenza, kidney ailments, anemia and low hemoglobin levels, infections such as Hepatitis B and C, Human Immunodeficiency Virus (HIV), psoriasis, as well as (preventive) vaccines for paediatric use.

3.1.2. Age

The age of CTPs in the sample ranged from 24 years to 75 years. The number of CTPs in the 41-60 years group was the maximum at eleven, followed closely by ten persons in the 26-40 years age group. Six participants were in the age groups of 0-25 years and 61-75 years respectively, with no information available for two respondents. Age related information along with other variables such as gender, education levels, etc., was collected to gain an understanding of any possible variations in experiences as CTPs. In the context of paediatric trials, the age of the two children whose parents were interviewed was 14 months.

3.1.3. Literacy levels

The study sample of CTPs reflected reasonable levels of literacy. Of the 36 CTPs, 33 had undergone some formal education, with no information available for three of them. Fourteen of the 36 had completed between 8th and 12th standard schooling, followed by ten who had completed their graduation, one had discontinued at the undergraduate level while three were post graduates. Three of the participants had studied 5th to the 7th standard and one participant till the 2nd standard. Information about education was collated for analysis of variability regarding access to information, comprehension of information in the course of clinical trials, particularly with regard to consent processes prior to and in the course of participation in clinical trials.

3.1.4. Religious and caste profiles

The clinical trial participants who were part of the study were from diverse religious and caste backgrounds. Although a majority of the participants identified as Hindus, respondents were also from Muslim, Jain, Parsi and Christian religious backgrounds. Similarly, with respect to the caste backgrounds of participants, a majority of those who identified as Hindu, belonged to the “general” category, and four identified as “scheduled castes (SC)”, of which one identified as Dalit Christian and two from “other backward classes (OBC)”. It appears from the data that all persons from all castes are participating in clinical trials. Though a large proportion was from the general category, some from the sample identified as SC and OBC, indicating participation in clinical trials by castes that are recognised as socially and economically vulnerable, although they may include those who are relatively better off.

The variable of caste is very complex, which needs further exploration and analysis in the context of participation in clinical trials. However, from the interviews it appears that people from all castes are participating in the clinical trials.

3.1.5. Work/Occupation

The participants in the sample were found to be engaged in a variety of occupations. Information about work/occupations was explored to understand the implications of participation. This also highlighted pathways of recruitment of participants and the vulnerability of the participants. For example, four participants, who were involved in sex work, were associated with a non-governmental organisation (NGO) that worked with sex workers, through which access to the former was possible.

The work or occupation of the CTPs can be categorised into primary, secondary, service and others.⁴⁴ One participant was engaged in farming, ten were involved in a range of businesses/enterprises – running a butcher’s shop, railways catering, decorating for weddings, garments and yarn business, etc. Fourteen CTPs were involved in the service sector, and worked in banking, as medical representatives, teachers, in a tele-communication company, as a cook in households, as sex workers, an operator at a marble processing unit, etc. Eight of the participants were either students, homemakers, retired, and helped family members in their work – such as running a tea stall, a grocery store, stitching of garments. Two of the participants were children, whose mothers were the participants in the study; both women were homemakers. No information was available for one participant.

3.1.6. Marital Status

Information about marital status was sought as this may have implications for decisions regarding participation in clinical trials, in processes of consent, and others. Twenty three of the CTPs were married and lived with their spouses. Six of the participants had been in marital relationships but their spouses had passed away, or were currently separated from them, or living in a different place due to their work. For example, one of the CTPs, who was a sex worker lived in a city, away from her husband and child who were living in their native village. Six of the participants were never married and no information was available for one participant. At least two

CTPs expressed close links between marital status and the health problems that they were experiencing, causing them to remain unmarried or separated from their spouses. Such situations may well provide the motivation for participation in clinical trials; the gendered nature of the linkages was also apparent from the narratives and necessitates further analysis.

3.1.7. Income and assets

Information about income and assets was sought from all the CTPs. However, information on incomes was provided by about 56 per cent of the respondents. Information on assets was provided by about half of the CTPs. The wide range in the incomes of CTPs was apparent from the data, with most incomes falling within the range of Rs 5,000-20,000 per month. One participant stated his monthly income as Rs 500,000-600,000. About four CTPs, including two women had no earnings and were financially dependent on other members of the family. The information was expected to lend to an improved understanding of the economic compulsions for participating in clinical trials, as well as to explore post trial implications.

3.1.8. Type of family

Information related to family type was collected primarily to understand implications, if any, for decisions regarding participation in clinical trials. For the purpose of analysis, the family was categorised into single, nuclear and joint family. “Single” family means where an individual lives all by herself/himself. “Nuclear” family is one in which the individual lives with her/his spouse and children or the individual lives with her/his parents, siblings. “Joint” family means that the individual lives with other members of the extended family- parents, mother-in-law, sister-in-law, brother-in-law, sister, etc. Among the 36 participants, at the time of the interview, 15 were living in nuclear families, 12 were staying in a joint family set up and three were staying on their own.

3.1.9. Location of residence

A majority of the CTPs, around 86 per cent lived in cities with two participants living in towns and three in villages in the four states where the study was conducted.

While a majority lived in the same city as the institution where the clinical trials were taking place, six of the 36 participants lived in another state, city or at a substantial distance from the institution and had to travel a fair distance to participate in the clinical trial, with implications for remuneration of CTPs. Many of the participants in the towns and cities lived in the slums or in resettlement colonies and lower income residential areas.

3.2. Profile of CTPs as shared by the KIs from the study sites

While the interviews with the CTPs provided critical information about their backgrounds towards analysis of their perceptions and experiences as CTPs, the discussions with the KIs also provided important information about the overall profile of CTPs based on their experiences of recruiting and conducting clinical trials. For this purpose, information was collected from various KIs. Selection of participants, according to the above, was dependent on the eligibility/inclusion criteria mandated for each clinical trial. Thus, the profiles of the participants based on the disease profile for which the clinical trial was being conducted, the location of the clinical trial, nature of the institution or hospital (private or public), which is conducting the clinical trial, etc., varied with each trial.

The profile of the participant depends on the requirement of the trial and its inclusion criteria. We do get participants from a wide array of socio-economic backgrounds. Participation also depends on the type of drug and the disease for which the trial is to be conducted. For instance, in cases of oncology trials, we have quite a few patients from high socio-economic class. [MHPI1]

According to a PI from Andhra Pradesh:

For Cardiovascular disease (CVD) usually the participants are mostly above 40 years of age with more number of males than females. This is with specific reference to CVD participants, but for other trials I do get participants from mixed profiles in case of COPD. [APPI4]

Most of the PIs said that participation of women and men was equal in clinical trials:

I do trials related to Cardiology. My patients are a mix of both male and female and their educational qualifications range from very educated to not-educated. The former are often more interested to participate in trials as they are well-read and are interested to know about new treatments. [GJPI1]

One PI had a difference of opinion:

Generally, I get more male participants for the trials than females. Usually, women are [more] reluctant to take any risk and are afraid to participate in any trial. I get people from mixed socio-economic levels. So depending on the eligibility criteria of any trials, I select them. [MHPI2]

Variance was also observed in the income and the literacy levels of CTPs, based on the information provided by the KIs from the different study sites:

The patients are men and women belonging to varied educational and religious background, but all of them belong to the lower income group. [APPI4]

The participants who come to our hospital are fairly well educated and from middle to upper-middle class. Many patients also come from economically backward classes. [DLPI1]

Things have changed a lot in the last five years. Earlier, people from lower socio-economic backgrounds would enter into clinical trials in lieu of free treatment. However, with increased media intervention, we have found patients across class backgrounds asking us more and more questions about participation in clinical trials. [GJCRC2]

The profile of CTPs was also determined by the varied recruitment processes carried out by hospitals, CROs, etc. For example, for some clinical trials, a majority of the CTPs may be recruited from a particular location:

CROs that do in-house trials are mostly doing volunteer studies. For that, they have to go out and get subjects. They use different methods such as

asking their agents to talk to people in the slums, mostly targeting the unemployed. Sometimes this may be done for Phase III trials also, particularly, in stand-alone trial sites. [CRO1]

Participants were mostly recruited from clinics/hospitals, thus the profiles of the CTPs varied with the type of clinic/hospital approached. The profiles of 36 participants (23 men and 13 women) presented in the chapter provide insights into the diverse backgrounds of the participants in the study and also provide the basis for a nuanced analysis of their recruitment pathways, reasons for participation, experiences as CTPs, which are addressed in subsequent chapters.

Recruitment

The first interaction between the clinical trial team and the prospective clinical trial participants (CTPs) occurs through the process of recruitment. This process of recruitment depends on the research design, cost, and time factors, which influence the study. Patel (2003) quotes Hulley and Keith in highlighting the two main goals of recruitment as follows:⁴⁵

To recruit a sample that adequately represents the target population; and to recruit sufficient participants to meet the sample size and power requirements of the study. (2003:229)

Thus, ensuring representativeness and ensuring an adequate number of CTPs are two main goals of the process of recruitment. The process of recruitment takes place in various stages. Defining the first step of recruitment, Patel (2003) writes:

It is the dialogue which takes place between an investigator and a potential participant prior to the initiation of the consent process. It begins with the identification, targeting and enlistment of participants for a research study.⁴⁶

Recruitment for any clinical trial depends on the type of research design and the medical condition of the participants. So enrolling eligible participants requires a properly planned study design, an effective screening process, the provision of meaningful and easily understandable clinical trial information, and the investment of appropriate cost and time. Until the past few years, independent clinical investigators initiated clinical trials, recruited participants, and interpreted and reported the results. More recently, there has been a substantial increase in the size of clinical trials to ensure that results are reliable and are not influenced by the play of chance.⁴⁷ The increasing number of clinical trials has led to the emergence of contract research organisations (CROs) and site management organisations (SMOs) as important players in the conduct of clinical trials. They are now coming more and more to the

fore and offering expertise acquired by working with specialist institutes to review demographic factors and historical data before initiating a recruitment programme.⁴⁸

Many sponsors, CROs, research institutes, medical colleges and hospitals have started employing clinical research coordinators (CRCs), pharmacists, and data managers to facilitate the conduct of clinical trials. Some CRCs based in hospitals may be employed directly by clinical trial sponsors to optimise the collection of data and to facilitate the conduct of the trial. Other CRCs are employed by hospitals with the goal of managing the clinical trial process, including making submissions to the Ethics Committee (EC), recruiting patients, monitoring the collection of data, and supervising the follow-up of patients who have been recruited for trials.⁴⁹

Surrounding this complex arrangement governing the conduct of clinical trials, where the principal investigator (PI) may not be the first person whom the prospective participant meets, are various concerns about how CTPs are recruited, and how data is analysed and reported. Recruitment methods for clinical trials vary from physician referrals to the use of highly specific databases of patients to mass media advertising.⁵⁰

In this context, one of the major objectives of this study was to examine and understand the route that leads CTPs to the clinical trial and ways in which the participants were recruited.

4.1. The route to the clinical trial

It is necessary to understand the different paths taken by patients to avail treatment and their reasons for doing so before we start exploring the process of actual recruitment. It was seen that patients make their way through a complex route of consultations with and referrals by multiple doctors, friends, family members, and relatives. Four of the participants from Andhra Pradesh interviewed were diagnosed with psoriasis, an autoimmune disease that affects the skin. Their desperation to seek relief is reflected in the multiple avenues and methods that these participants tried and explored. They went through a series of doctors and tried various forms of alternative treatments, including ayurvedic, herbal, and healing (praying) to get cured, but to no avail. All the four participants landed up in a government hospital where the

doctors suggested that they should participate in an ongoing clinical trial on psoriasis. One of the participants described the trajectory of treatment:

My mother went to the church and prayed to YesuKreestu [Jesus Christ]. She even took me to a bigger church, which is very famous, in the nearby town. She took me to the naatuvaidyudu (local healer). He used some pasarlu [paste of medicinal plants], but it did not give me relief. I visited two to three local private doctors in my district, but those medicines did not help me much. Then I moved from allopathy to ayurveda medicine for some time. One day, I went on work to another town and stayed with my relatives . . . I told my relative . . . about my problem and he suggested that I visit the medical college for treatment. I decided to go there and registered in the OPD. I was examined at the dermatology OPD . . . though the treatment gave me minor relief and my skin problem was almost the same. Last year, during the OPD hours, the doctor told me that there is a new drug on trial for psoriasis, which was to be tested on psoriasis patients and they are conducting the trials in the department. The doctor asked me whether I would be interested in participating in it. But this does not mean that we have stopped trying alternatives. We still visit religious places and offer prayers simultaneously. [APCTP1]

Similarly, the other CTPs also went through many alternative treatments and adopted various dietary restrictions. According to another participant:

Since it was a skin problem, I was not sure about [the wisdom of] speaking about it. Once the patches became visible, I was very scared and thought I must have got leprosy. I told my sister, who took me to the local doctor in our basti. We did not have money to go to a big hospital. The medicines and the ointments that he gave did not give me any relief. We went to the local healer. He gave me some herbal medicines and I used them for some time. I was asked to go through major dietary restrictions like avoiding eating brinjal, yam, eggs, meat, etc. I tried everything. We even offered prayers regularly to many gods, particularly to the goddess who cures skin problems, smallpox, etc. Nothing helped. [APCTP2]

Another participant from Gujarat said:

I had first visited my local doctor, but his medicines did not show any effect. I was worried and even my family members were concerned. My relative suggested that I should go to a homeopath. One never knows what is going to work. [GJCTP3]

A few CTPs spoke about accessing alternative treatments on either being advised to do so by family members, relatives, or friends, or because they were desperate and were willing to do “anything and everything” to get cured. It is also an important indication that when it comes to treatment for, say, a specific problem like psoriasis, allopathy is not the only domain of “treatment” accessed by patients. What it also reflects is that the strong desire for a cure often leads the patient to access all kinds of “treatments”, without exercising much discrimination. In the entire trajectory, these forms of alternative treatments are deemed to be as significant as allopathy. This belief is combined with the general perception that one never knows what is going to work, which is again reflective of the hope of getting well. A participant from Gujarat said:

Initially, we visited many private doctors locally. They gave me some medicines and ointments for application, but these did not help. We also spent quite a bit of money. Every doctor used to say it will take time, but no medicine worked. Then my sister insisted on taking me to the government hospital in another district. . . . I visited the OPD every month and the treatment continued for two years . . . It was in February last year [2011] that the doctor told me about a trial. [GJCTP18]

The above experience also highlights the fact that in the process of these multiple consultations, the patients also spent a significant amount of money driven by their desperation to get relief. Hence, when they are told about a “new treatment”, especially one that will be “free”, the chances of them agreeing to participate in the clinical trial increase. A participant who was referred by an NGO described her journey to recruitment in a clinical trial as follows:

When I was diagnosed with HIV/AIDS, I approached the NGO that is working with sex workers under the HIV prevention programme for the

last fifteen years in our area. The NGO representatives referred me to the government hospital. I was not sure about the government hospital because of the way they treat us in OPDs. I went to a private clinic, but it was too expensive. Then it was suggested that I visit this doctor who was a renowned doctor for the management of HIV amongst sex workers. The doctor informed me that there was a clinical trial going on for the prevention of cancer and referred me to a hospital for this trial. [MHCTP9]

In all the cases, the patients tread on multiple and sometimes simultaneous treatment paths, such as prayers, home remedies, visiting local healer, homeopaths, hospitals, etc., and then get enrolled in the clinical trial. A participant who was diagnosed as diabetic eight years ago, and who also suffered from hypertension, was referred to the same cardiologist his father was consulting:

I am a juvenile diabetic patient and was diagnosed with diabetes eight years ago. For my treatment, I usually visit a diabetes expert close to where I stay . . . Two months back, as I was driving back home from my tuitions, I suffered from intense chest pain, as if somebody had torn my heart from inside. Then my father took me to a cardiologist in the same city . . . Since the [test] results were abnormal, the doctor referred me to another doctor. My father is also a heart patient and he also takes treatment from the same doctor I was referred to . . . this doctor successfully treated my father without any surgery. So my family knows this doctor very well and also we trust him immensely . . . The doctor told me that fat levels in my blood are high due to some infections in my arteries. He suggested a new improved and free treatment that I could consider. [MHCTP4]

In the above case, the doctor was well known to the patient and had been treating his father too. The patient had approached the doctor for treatment for his condition. Later, when the doctor advised the patient about the clinical trial, which the patient saw as new and free treatment, he concurred because he had immense trust in the doctor.

Patients may also stop different treatments at different points, only to re-continue some treatments when they are ready again, either financially or otherwise.

Thus, the treatment process was fluid, with many systems of medicine being accessed at once, with many switches being made between these systems, and with several providers being visited and doctors being consulted, all of which was motivated by the desire to leave no stone unturned in the quest for a cure.

Thus, the path to clinical trial recruitment is based on desperation on the part of patients to receive treatment, leading them to consult many doctors for relief and to try new options at the referral of doctors, friends, and family members. In this process, patients also spend a considerable amount of money on consultations and investigations. After undergoing all this, when something new, improved, and free is offered to them, they see it as an attractive option, and hence are willing to participate. This willingness makes them suitable participants for clinical trials.

4.2. First point of contact

Since the patients were recruited from the hospital Outdoor-Patient Department (OPD) and the Indoor-Patient Department (IPD), the first point of contact for them were mainly the doctors. A participant from Gujarat said:

When I went to my doctor, he referred me to this hospital. At this hospital, I was informed that I had symptoms similar to Hepatitis C. Thereafter, the doctor told me about an ongoing trial for Hepatitis C. The doctor who examined me in this hospital informed me about the clinical trial. For further information about the trial, I was sent to the medical officer in charge of the clinical trial. The medical officer explained the details of the study—voluntary participation, right to withdraw from the trial any time during the course of the trial . . . Most of the time, I interacted with the medical officer or the CRC present there. [GJCTP3]

Other than the doctor, participants also recalled getting in touch with the PI in charge and the CRC while being part of the clinical trial study. A participant said:

He [the doctor], in turn, referred me to the CRC in this hospital for the injections. We had a brief discussion, following which I got my urine, stool, and blood tested. Thereafter, they began administering the injection. [GJCTP12]

Similarly, a participant from Andhra Pradesh said:

The doctor first informed me about the trial. Then she suggested that her junior doctor and the CRC should talk to me and explain [everything] to me in detail. I was convinced and decided to be a part of the trial. [APCTP4]

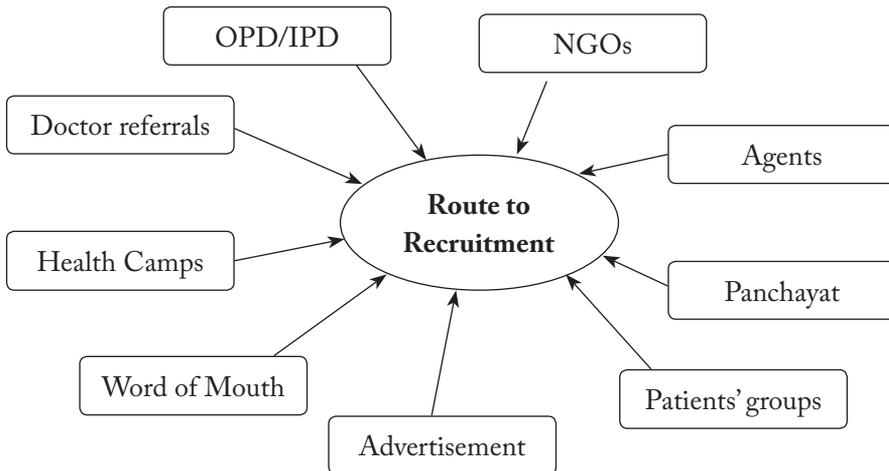
A participant from Gujarat said that earlier she had volunteered for a clinical trial study, but could not clear the screening procedures. The hospital contacted her the second time after retrieving information about her from their database. In her words:

I had been a part of a clinical trial that studied the prevalence of G6PD deficiency amongst [the] Parsi community in India and the correlated diseases caused by this deficiency. One day, I got a call from the hospital saying that they wanted me to participate in [another] clinical trial. [GJCTP19]

4.3. Patterns of recruitment

After analysing the data obtained from the CTPs and from the key informants (KIs), it can be stated that the most common avenue of patient recruitment is mainly through the OPD and the IPD, in comparison to the other recruitment methods such as recruitment from a health camp, or through advertising, or from local communities through panchayats, patients' groups, and community based organisations/NGOs.

Figure 4.3.



4.3.1. Recruitment from OPDs and IPD

The majority of the participants said that they were told about the trial when they visited the OPD for treatment or were admitted in hospital for treatment. A participant from Andhra Pradesh said:

I used to visit the OPD every month and the treatment continued for two years. It was in February last year [2011] that the doctor told me about a trial, that they were testing a medicine for my problem not only in India [but] even in other countries. [APCTP2]

Another CTP narrated:

During my pregnancy, I used to visit the OPD of a government hospital for my check-ups. As my due date came closer, I got myself admitted in the maternity ward of the same hospital. At the time, a doctor approached me and told me about this 'single injection' that could protect my child from six diseases. He also told me that it was a special injection, which was being tested, and that they were giving to 100 selected children. If I agreed to use this injection, it would be given for free. He told me that if I

was okay with it I should come back with the baby within 45 days after the birth. I was not sure what I should do. I told my husband about what the doctor told me. In a few days I delivered a boy and went back to the doctor. [APCTP5]

In the process of recruitment the doctors benefit from their experience of practising in a particular field or area of specialisation. They see a large number of patients every day and develop a relationship of trust with the patients. Hospitals with multiple specialties are also at an advantage because they have patients with varied profiles. A PI explained how he recruited patients for clinical trials from the OPD:

All my trial subjects are from my own clinic OPD. I have extensive experience of forty years in practising medicine. So, naturally, I have a large network of patients, so I never have a problem in recruiting participants. In addition, since my hospital has other skilled doctors from various branches, we do take up clinical trials for those diseases also. [MHPI2]

Similarly, a PI from Maharashtra said:

I recruit patients from my OPD. Since I have a large pool of patients in my OPD, I can easily recruit patients . . . I have been practising in this city for a long time, so I know most of my patients. [MHPI2]

The doctors also develop a network with other doctors. So, information about any given trial reaches various doctors and they refer patients to each other, depending upon the specific requirements of a clinical trial. A principal investigator from Delhi elaborated:

Research subjects are sourced through the OPD and referenced from other doctors. We speak with other doctors in the hospitals and ask them to refer to us any other participants who appear to fulfil the criteria. We share with them a snapshot of the trial so that they can help us in the recruitment for the clinical trials. [DLPI1]

Government hospitals have large numbers of patients in the OPDs of their various departments. A principal investigator from a government hospital in Andhra Pradesh described this:

The government hospital is quite big and we get a lot of patients in the OPDs and IPDs. It is easy for us to recruit subjects since we have a large pool of patients here in the hospital. And I personally get a lot of patients in my OPD every day and I can select the subjects and recruit them for any clinical trial. It is never a problem for me. I personally select subjects from my own OPD for my trials . . . We know our patients very well. That is the advantage of a public hospital. We have a good rapport with all the patients as we interact with them personally. We don't have any middlemen talking to the subjects about trials for their recruitment as it happens in private hospitals. No agents. [APPI4]

This availability of a “large pool of patients” is one of the reasons for recruiting participants from the OPD/IPD.

However, it was interesting to note that some of the sites recruited patients enrolled under the Arogyasri⁵¹ insurance scheme in Andhra Pradesh. According to a PI:

We have [the] Arogyasri health insurance scheme in our state in which poor patients from BPL [below poverty line] families can access treatment from both public and private/corporate hospitals for certain health problems free of cost. I have seen many Arogyasri patients with cancer who required treatment. However, they were not in a position to continue because of their poverty. As far as I know this treatment was not covered under Arogyasri. I knew that a hospital in Hyderabad had recruited one Arogyasri woman patient in the trial of cancer drug in the past with a good intention as she would get free treatment because she could not afford it otherwise. Apparently, the PI received a legal notice for conducting the trial on an Arogyasri patient. I still feel that the oncology trials will benefit poor patients. [APPI2]

AROgyASRI PATIENTS TURN GUINEA PIGS

Roli Srivastava & Bushra Baseerat, TNN

Feb 10, 2011, 05.57am IST

HYDERABAD: The poor literacy level of Arogyasri beneficiaries has given a lucrative but worrisome spin to [the] healthcare business in the state-city hospitals [that] are now hard-selling their patient numbers to bag clinical trial projects from international pharma firms. Whether big or small, public or private, most hospitals in the state now have a dedicated clinical research unit to carry out trials. Doctors note [that] there is a surge in the number of companies headed to the state and also the number of trials being carried out, "because there are a lot of guinea pigs here". Being tested on people are drugs for diabetes, [and] cancer apart from drugs for cardiac, gastro and liver conditions. Certain drugs for hormonal problems as well as rheumatic disorders are also being tested currently in city hospitals. The trials are on even in district hospitals, both private and public and doctors involved in clinical trials agree that most of their volunteers are 'uneducated and poor'. There is reliable information on [sic] poor patients [are] even being 'supplied' to hospitals under Arogyasri for the trials. "Getting a signature on the consent form is not difficult. If it takes a year to get 10 patients to volunteer for a trial in the US, here the same number can be arranged in no time," said a researcher.

Source: [http://articles.timesofindia.indiatimes.com/2011-02-10/hyderabad/28546457_1_trials-account-clinical-trials-city-hospitals] accessed on 13 October 2013.

Though the intention of the PI may be to make the trial drug available to the Arogyasri patient, there are many media reports which exposed the way some of the Arogyasri patients were recruited for clinical trials of various drugs without any proper consent.

4.3.2 Suggestion by friends, family members, and other relatives

A participant from Gujarat who was suffering from obesity stated that his friend had advised him to participate in an ongoing clinical trial. The CTP said:

I came here for my weight-related problem. My friend, who was my roommate, informed about an obesity trial which was going on here [in this hospital]. He suggested me to try it, so I came here. I came into contact with the CRC and met the doctor here also, but right now I don't recall his name. [G]CTP5

Another participant from Gujarat was introduced to the doctor conducting the clinical trial by her brother-in-law, who worked in the same hospital:

My brother-in-law was working in a hospital where the doctor who is doing this trial was a consultant. My brother-in-law helped me get in touch with the doctor. I met the doctor and told him about my health problems and since then I have been under the doctor's care. It is now almost one and a half years. [GJCTP13]

The health-seeking behaviour of patients varies across individuals. However, the general trend observed was that either the patients had been consulting the doctor conducting the clinical trial for a long time or they had been referred to the doctor by someone they trusted, such as a family member, family physician, friend, or a relative.

4.3.3. Camps

In Gujarat and Maharashtra, the camp approach was seen more popular alternative as compared to Delhi and Andhra Pradesh. Three KIs claimed that they source participants from health camps, which are organised by the hospital in nearby villages and towns. A CRC from Gujarat said:

We have conducted some camps to recruit patients for clinical trials where we did not get sufficient patients. Usually, these camps are not very helpful in recruiting patients for such trials. Camps and advertisements don't help much, as all kinds of people come for them, despite being informed that the camp will only be for people having a certain kind of illness. So we hardly get one or two patients with the help of camps. There is also a lack of commitment from the patients who are recruited through camps. They come for the camp considering the free service in the camp, but once they are asked to come to the clinic and get enrolled in the trial, they back out. [GJCRC3]

According to a PI:

We organise health camps in rural areas and in suburban areas for health checkups. During the checkups, we identify patients and ask them whether they would like to be a part of the trial. [GJPI2]

A participant who was from Maharashtra informed about the clinical trial by a doctor when she attended a medical camp.

She said:

At the camp, a doctor informed me that since I was a sex worker with multiple partners, I was more prone to develop cancer. He advised me to get myself screened for the disease through these trials. And if [cervical cancer is] diagnosed, they would also treat it with proper technology and treatment. [MHCTP7]

Another participant from Gujarat said:

This hospital held health camps in our area. They did physical check ups etc in the camps. I had a heart problem and they have asked me to enrol into a trial in their hospital where I can be treated with a new drug. [GJCTP17]

4.3.4. Non government organisations

Some participants explained that often researchers from different hospitals, colleges, etc., visited areas where sex workers stayed and looked for local NGOs and agents who worked with sex workers. One of them said:

I was approached by a researcher from a hospital through an NGO who works with sex workers in this area. [MHCTP7]

Another CTP from Maharashtra said:

We were approached by a hospital through an NGO which works on HIV/AIDS to be a part of some study on cancer. [MHCTP9]

4.3.5. Panchayat

One of the participants from the Parsi community in Gujarat said that a lady doctor from Mumbai had contacted their local Parsi panchayat for help in conducting a study. The panchayat had invited the community members to take part in this study.

4.3.6. Patients' Groups

Some KIs took another route to recruit from patients groups for clinical trials. A participant from a patients group in Delhi said:

Sometimes we get to know about clinical trials through different sources, sponsors, and hospitals. [DLCTP1]

4.3.7. Others

A representative from a CRO said that some CROs employ agents and SMOs for recruiting trial participants:

They [CROs] use different methods such as asking their agents to talk to people in the slums, [while] mostly targeting the unemployed. Sometimes, this may be done for Phase III trials also, particularly in standalone trial sites. Very rarely is such a process followed in hospitals. Earlier, sponsors used to hire SMOs to do this kind of work and sometimes they used to hold a lot of medical camps to recruit participants. However, nowadays, SMOs only manage trials in hospitals and work within the hospital setting. [CRO1]

4.4. Inclusion and exclusion criteria

The process of patient recruitment is guided by inclusion and exclusion criteria of the research protocol. The KIs shared their views about the criteria and explained how these varied with the nature of any given study. The selection of participants for the study depends on these criteria. The criteria are set prior to the start of the study. Different KIs had different levels of information regarding these criteria. Speaking about the inclusion and exclusion criteria, a sponsor from a pharma company said:

The scope for including and excluding patients lies entirely with the investigator, and it is for the Ethics Committee to determine [the] criteria. Asking the sponsor about what kind of patients you want for conducting your trials is not a question I will be able to answer. Because for me, any patient who qualifies medically for participating in the study can be recruited, i.e., anybody who meets the requirements as per the protocols,

[who] signs and gives the informed consent form is good enough . . . The ability to have patients come back for follow-up is also generally seen in educated patients who have a better understanding of their health needs. These are things that are not particularly stated in [the] GCP [Good Clinical Practice] or [in the] other guidelines, but 'smart' investigators can possibly follow [them] in their centres to ensure that the kind of patients they recruit can be sustained over the period of the trial. [SP]

Although the criteria and the protocols are set by the sponsor and approved by the EC, it is the PI and to some extent the CRC who are responsible for the actual implementation of these set protocols. Describing the criteria for his study, a Clinical Research Coordinator from Andhra Pradesh said:

There are inclusion and exclusion criteria for the selection of the subject . . . the previous history of congenital diseases, the family background in terms of health, like cancer, heart problems, epilepsy, etc. For example, for the present trial, we take patients who have three years of history of the disease. Also, [patients] who are,

- *willing to come for the subsequent shots/drugs during the trial period*
- *willing to give their consent*
- *willing to give their blood sample, etc.*

And, of course, the protocols should be approved by the EC. [APCRC2]

Providing details about the inclusion and exclusion criteria for his study, a CRC from Gujarat said:

The PI usually has all the inclusion and exclusion criteria at his fingertips. Inclusion and exclusion criteria are set prior to the start of the study. For example, if it is a trial of a diabetes drug, the criteria may include the level of HBA1C. If it is 7–10, then it is moderate, and severe is 12–13. Depending on the drug trial, the patient with the requisite level will be selected. Apart from this BMI may be a criterion in a diabetes trial. The

age criterion may be up to 65 years to increase the probability of [recruiting] patients for trials. Sometimes patients are selected because they meet all the criteria, but when the lab reports come back to us there might be some levels that are not within the selection range. In 10–20 per cent of the cases, if the levels are only slightly above or below, the patient may be given medication for the problem, and once the levels reach 'normal', [the patients] can come back and get recruited for the trial. When the patients come back, then the entire process is followed again, including [the process of] informed consent. This is treated as a new application. [GJCRC1]

Speaking about the caution exercised in selecting patients, a PI from Maharashtra explained:

Protocols generally do not recommend screening for HIV. In case of clinical suspicion, doctors are asked to avoid taking these patients. Any screening for HIV is done as per [the] NACO guidelines counselling, consent and then the patient is either included or excluded as per [the] protocol. No false assurances are made. [MHPI4]

A principal investigator from Andhra Pradesh explained the process of recruitment and described the inclusion and exclusion criteria. When asked how he recruited clinical trial participants, he replied:

We just closed this trial, so I can give you details on this. We have conducted [a clinical trial] on 90 children following inclusion and exclusion criteria. Some of the children who were a part of the study were born in the IPD of the hospital itself and some [were recruited] from the OPD. Since it is a government hospital, a large number of patients visit it, and it is not very difficult to speak to pregnant women or expectant mothers at the gynae ward or with the parents of the newborn children in the paediatric ward.

He further stated:

Why should they not get access to these trials? If we do it ethically, without any profit motive, we can conduct [trials] on the children from our own OPDs. [APPI5]

4.5. Difficulties in recruitment

The KIs explained not only the process of recruitment but also the difficulties faced by them in recruiting participants for clinical trials. Some KIs said that it is not easy to convince patients to participate in clinical trials. According to a CRC from Gujarat:

It is very difficult to recruit patients for placebo-controlled studies. There was one study in which the protocol demanded that severe patients be recruited. However, the DCGI intervened and changed it to patients showing moderate indications of the disease. The DCGI argued that if one were to recruit severe patients in a placebo-controlled study, then there was a chance that the condition of the patient may deteriorate and the patient may expire. This would only make the sample size go down and as such it would be difficult to assess the effectiveness of the study. [GJCRC2]

A sponsor described his experience:

We were doing a study on tineacapitis, i.e., the fungal infection of the scalp. We suddenly got a call from one of the sites saying that there are ten–eleven patients available. When we asked them where these patients were from, they said they were from a girls' orphanage. But we decided not to recruit them because these people as per your definition would be vulnerable. And once they are classified and we know that they can't consent in an informed manner, then it may raise ethical concerns. This is an example of a restraint that a particular investigator, etc. or a sponsor or a CRO will have to imbibe. [SP]

Indeed, some KIs very clearly discouraged non-literate patients from participating in clinical trials or made it mandatory for them to bring along a witness who was literate.

A principal investigator explained:

People in India are not aware of clinical trials and hence it is difficult to make them understand the benefits associated with clinical trials. Anything related to the word 'trial' makes people suspicious and they feel they are being experimented upon. Here we have a denial rate of 50 per cent to 60 per cent of the patients we shortlist as subjects matching the inclusion criteria of these trials. [GJPI4]

Some KIs said that without sufficient patient retention from the time of the initiation of the clinical trial to the time of its completion, one cannot derive any conclusion proving or disproving the goal of the clinical trial sponsor.

A sponsor elaborated the difficulties PIs face during the recruitment process:

If I have a one-year study, I need to have patients on the drug for, say, the first six months and the next six months are for follow-up visits, say, once every two months and so on only to evaluate the progress. This is possible only with responsible patients. Thus, the ability to have patients come back for follow-up is also generally seen in educated patients who have a better understanding of their health needs. These are things that are not particularly stated in [the] GCP or [in the] other guidelines, but smart investigators can possibly follow [them] in their centres to ensure that the kind of patients they recruit can be sustained over the period of the trial. For example, if he recruits a hundred patients and ninety of them are uneducated and will not know the importance of these things and will not bother to follow up after that, since, as I mentioned earlier, patients do not get compensated for participating in trials, what they may get compensation for is only their travel that they may be expected to undertake for the trial per se. [SP]

Discussion

The experiences and perspectives of CTPs revealed that in most cases, patients were recruited by PIs from their regular patients through OPDs, IPDs, and health camps.

Given that the recruitment of participants was from OPDs/IPDs by the KIs, it is not surprising that the first point of contact for the participants was the doctor they consulted for their medical condition. Most of the participants mentioned that they became a part of the clinical trial process because of the doctor they were consulting for treatment. When a primary caregiver becomes the researcher, the patients may feel obliged to participate in the clinical trial, believing that otherwise the doctor may not pay attention to them in the future. This situation also increases the chances of therapeutic misconception as the patients are from the OPD undergoing treatment and the doctor is advising them to enroll into the clinical trial as one of the option with added benefit of no cost. Here, the doctor's ethical and moral duty was to clearly and emphatically inform the patient, in no uncertain terms, that it is "an experiment" and not a "new treatment", and that it may or may not work and that the drug can cause side effects. Thus, many issues arise even before the patients become clinical trial participants. The patients go through various referrals, spend money on treatment at various places and they reach to or are referred to the site of recruitment for clinical trial. When they are desperate to find relief through treatment, the doctor advises them clinical trial as one of the better and free treatment options and they get recruited in the clinical trials.

This blurs the boundary between the clinical trial and routine treatment. This also raises an important ethical issue about the vanishing line of demarcation between "standard care" and "clinical research". Highlighting this ethical issue, Kim (2012) writes:⁵²

Clinical research is not an individualised therapeutic activity and [is] carried out to answer a scientific question and [is] applied to future patients. Physicians and patients commonly fail to appreciate the distinction between research and therapy because of the similarity in the physician and patient relationship, especially with regard to the setting out of innovative or non-validated therapies. (2012:9)

Similarly, Chen (2003)⁵³ argues that physicians need to be careful and to understand the difference between standard clinical care and clinical research.

This recruitment practice can lead to many problems, including conflict of interest; exploitation of the vulnerability of patients seeking health care; and exploitation of the unequal relationships between physician/investigator and patient/participant. Due to rampant poverty and lack of free medical facilities, participants opt for trials driven by desperation, because as far as they are concerned any treatment is better than no treatment. While CTPs can be seen as the first to garner the advantages or benefits of a new medical procedure or development, they are also the first to subject themselves to the unknown risks of an untested drug. This situation also raises concerns about the possibility of the subtle coercion of such patients to enrol in clinical trials.

While no country prevents physicians from being investigators and recruiting their own patients, some nations have instituted regulations to (a) separate the clinical space from the research space in hospitals; and (b) not allow physicians to obtain informed consent. There is indeed a conflict of interest in care-cum-trials that are mostly conducted in communities where poor and uneducated patients are enrolled as participants. It is difficult to imagine that patients under care will refuse to participate in a trial being conducted by their doctor.

Thus, it is essential that doctors and physicians who are also principal investigators or who are part of the clinical research team disclose their financial interest and the recruitment fees that they receive from the sponsor to the approving or accrediting authorities, the Ethics Committee, and other bodies, before the clinical trial commences. So that all conflict-of-interest issues can be addressed so that patients are not recruited due to the influence of the doctors/physicians, and so that their vulnerability is not taken advantage of by the entire research team, including the sponsors and the pharmaceutical industry. It is essential that the clinical trial participants make an informed decision about the clinical trial, and are not influenced by either monetary considerations or swayed by the doctor who may persuade them to participate in the clinical trial.

Reasons for Participation

Rarely there is a single reason that compels an individual to participate in a clinical trial; invariably, it is a combination of factors that motivates participation in clinical trials. The factors that influence the decision to participate may be divided into the factors that “push” individuals to be part of clinical trials and those that “pull” or attract them to enrol in these trials. The push factors include the economic and medical conditions of the person, altruism, and the views or influences of family and community. The pull factors include the inducement of receiving “free treatment” in the course of the clinical trial, priority in receiving treatment, having ready access to doctors, and the immense trust reposed in doctors by patients.

The following sections examine the various factors stated by the clinical trial participants in their interviews as the reasons for their participation in clinical trials.

5.1. Push factors

5.1.1. Economic status

Economic reasons are one of the strongest and most compelling push factors that influence the decision of patients to enrol in clinical trials because they cannot afford the available treatment for their disease or medical condition. This can push patients to participate in a clinical trial even though alternative treatment is available at a cost. Patients who can afford the alternative treatment may or may not enrol in the trial because its free, i.e., those who can afford the alternative treatment may not get “pulled” into participating in the clinical trial because it is free. Economic status, therefore, has implications for the voluntariness of consent.

Economic factors are central in pushing individuals into participating in clinical trials, because of the non-affordability of the available treatment for their medical condition. This point was made by a participant from Gujarat:

Due to low haemoglobin level, I used to feel very weak. I also suffer from diabetes. I then contacted a doctor and told him about my problem. The

doctor told me that I would need to take some injections for this. But the injections were very expensive and I couldn't afford them. He then told me not to worry and that he could provide the injections for free, if I participated in a trial. After four weeks I went again to meet him. [GJCTP12]

Another participant found himself in a similar situation. He decided to participate in the clinical trial as he could not afford the injections but needed to access treatment for his medical condition:

I did not think about it much. I knew that I could never have afforded the injection. So I decided to be part of the study. I did not have any idea about such studies till I heard about them. In my case, I was told that the injection would help me and that it was free. [GJCTP17]

According to a principal investigator from Delhi, most educated urban patients are not ready to participate in clinical trials and constitute only 20–30 per cent of CTPs. He has also mentioned that most of the patients recruited for the clinical trial are poor. Another PI from Andhra Pradesh said:

Ours is a government hospital and we get only poor patients in the OPD. Most of them are semi- and non-literate. They also come from nearby rural areas. We do get patients from all backgrounds, but the majority are from the lower and middle classes. [APPI4]

Thus, the economic status of participants along with the high costs of treatment are the major factors that influence their decision to participate in a clinical trial. The high costs of treatment, low incomes, economic dependency are push factors that increase vulnerability to participating in clinical trials. A participant's narrative elaborates this situation:

I have been suffering from kidney problems for almost two and a half years now. I started experiencing swelling [sujan] in my feet whenever I stood and cooked for longer stretches of time. I informed the lady for whom I cook—she is also a doctor. She advised me to get some tests done.

But at the time, due to my financial constraints, it was not possible to get the tests done or to go in for treatment because of the very high costs. I could not afford it. [GJCTP13]

It can be seen that the CTP could not afford the diagnostic tests that were recommended by the doctor. Subsequently, the possibility of receiving free treatment through participation in a clinical trial was sufficient to influence her decision to participate in the clinical trial. She elaborates that it would not have been possible for her to buy the medicines from the market, as they were very expensive. This does not imply that she would not have enrolled in the clinical trial if she could afford the diagnostics or the relevant treatment for her condition. Rather, she would have had a choice: either to enrol in the clinical trial or to pay for an alternative known treatment. However, her situation allowed her no choice but to enrol in the clinical trial in order to receive the treatment she needed, although it was not a treatment, but a “trial” or an “experiment” being conducted on her body.

Taking part in a clinical trial, however, also generates a cost burden for the participants, as a result of the expenses for travel, food, and accommodation that they have to bear, and the loss of working days as a result of participation in clinical trials that may necessitate a higher number of visits due to the elaborate processes of screening, medical examinations, etc.

5.1.2. Altruism

Along with the economic factors mentioned by participants, some of them stated that they participated in clinical trials also because they perceived their participation as benefitting others suffering from similar medical conditions. According to one of the participant:

I had some hope that this drug might help me and help others like me. [MHCTP2]

Another participant from Maharashtra said:

When the doctor told me about the trial and its benefit, I said yes. I felt I am also contributing to something that can help patients like me who are in search of treatment. [MHCTP1]

A principal investigator from Delhi said:

I have also had patients who volunteered to be a part of the trial. They think they have a role to play in helping find new, more effective treatments that can save many lives. We had many such patients who kept asking about clinical trials. [DLPI2]

Thus, according to the PI, some patients participate in clinical trials because they are motivated by their role in contributing to the process of exploring or discovering new or advanced treatments for the wider benefit of society.

A similar view was expressed by a CRC. He said:

The main motivation of the participants is the availability of free medicine that may make their condition better. Some of them also participate because they think that this may benefit research and other people like themselves. [DLCRC1]

Similarly, according to a PI from Delhi:

Some of my cancer patients, who are terminally ill, do enquire from me regularly whether we need any volunteers for drug trials. They think that any innovation might benefit others in the future. Thus, some patients think about helping others while participating in clinical trial. [DLPI1]

5.2. Pull factors

5.2.1. Free health services: free medicines and free investigations

“Free treatment” is one of the strongest pull factors influencing the decision to participate in a clinical trial. A participant from Gujarat was informed by the doctor that certain injections would help him and decided to be part of the study, as he could not afford the injections he needed for his medical condition. Another participant from Maharashtra said:

The factor that influenced my decision to participate in the trial was that free treatment would be provided to me for one year. Initially, I was very

apprehensive about the cost of the medicines, since I knew that the kind of disease I have, would require a very expensive treatment otherwise. He [the doctor] also told me that the only course of treatment available was very expensive. And on realizing my inability to afford such an expensive treatment, he informed me about a clinical trial of a drug to treat my condition. He suggested that I should participate in the trial. [MHCTP1]

As another participant from Andhra Pradesh said:

I told my husband about it [clinical trial]. My husband was happy that we were getting such an expensive teeka free of cost. A neighbour in our basti [slum] took her child to a private doctor to get the teeka. She paid a lot of money. My husband was happy as we were getting it free and because it would prevent our child from falling ill in future. [APCTP5]

Another participant narrated her experience:

I was six–seven months pregnant when I went to an NGO to ask them if they could refer me to any clinic for abortion. The NGO directed me to a hospital. At the hospital, the doctor advised me that it was too late and also dangerous to undergo an abortion. The doctor then suggested that I should participate in a new drug study so that my child doesn't get infected with HIV. I was undergoing a great financial crisis during those days, so I decided to be part of the trial as it would mean free access to the drug as well as free delivery of the child. [MHCTP6]

A principal investigator from Andhra Pradesh said:

For cancer patients, trials are like a boon because the treatment costs are very high, [but] which is free of cost for the patients in trials. Many are from upper-middle and middle-class backgrounds. Most of our subjects are from the middle class, the upper middle class, and a few are from lower-income groups. Even the rich come and ask us about any ongoing trials. Since the treatment is expensive, many show interest, as during the trial the treatment is free. There is also a hope that this new

innovation might help. Most of the trial subjects have insurance [private health insurance]. Still there are other costs, which may not be covered by the insurance. However, for cancer patients in clinical trials, there is a substantial advantage as one chemo injection costs Rs 25,000. Being a part of the trial, they get the drug free of cost. [APPI2]

A substantial number of CTPs, however, opt to be part of clinical trials, as discussed earlier, because of the lack of affordable alternative treatment options. Thus, any risks vis-à-vis participation in clinical trials are weighed against the benefits of “free treatment” in arriving at the decision to participate in clinical trials.

5.2.2. New treatment

Access to “new treatment” is also a great source of motivation for participation in clinical trials. Some CTPs stated explicitly that availability of “new treatment”, or even the promise of the availability of this “new treatment”, was the main reason for their agreeing to be part of clinical trials. As a participant said:

The doctor told me that the fat levels in my blood are high due to some infection in my arteries. He suggested a new improved and free treatment that I could consider. I thought that there was no harm in trying a new treatment since I anyway trusted the doctor. [MHCTP4]

Some of the participants enrolled in the clinical trials because their treatment at the time was perceived as not being effective, or was seen as not working very well for them, and they were very hopeful about the drugs being investigated or tested in the clinical trials. This perception was magnified or strengthened by the assurances given by doctors/PIs.

A programme manager at a hospital stated:

My feeling is that you can bracket it into different categories. In the case of an unmet medical need, such as for multiple sclerosis, Parkinson's disease, oncology, etc., any person will want to enter into trials. I get several mails from many US-based NRIs to find out if there is a trial going on for these diseases. If there are no therapeutic alternatives, everyone

wants it. That is the sad part—people who talk about these things are willing to come in when they want to save their own lives. When you talk to the same people about participating in a type-2 diabetes study, where they have multiple existing options, they are not willing. There they want someone else to take it up. People want ready made solutions. If I put a bottle in front of you and tell you it's an excellent cure for certain ailments, but has never been tested on humans, you would never want to be the first person on whom it is tried. [SP]

The participant profile mentioned by the programme manager is specific to clinical trials for a certain profile of diseases for which improved drugs are constantly being sought, and by a certain profile of CTPs, for example, US-based NRIs. Hence, the representation by researchers or the recruitment team of the “new treatment” as “very promising” or as “guaranteed treatment” misleads patients into buying into the idea of participating in clinical trials. This is a clear and deliberate violation of the ethical code of conduct governing clinical trials.

5.2.3. Trust in the doctor: Influence of the doctor–patient relationship

Another strong pull factor is the doctor’s influence on the patient’s decision regarding participation in a clinical trial. This influence emanates largely from the typically hierarchical relationship between doctors and patients, as well as from the trust reposed by the patient in the doctor’s judgement with regard to the latter’s health, treatment, and well-being.

A participant from Maharashtra said:

Once we are in the doctor’s hands, we surrender ourselves to them so that they decide what is best for us, finalizing our treatment, as we are ignorant and do not understand anything about this. [MHCTP3]

Similarly, a PI from Maharashtra said:

If I explain to them [patients] about the clinical trial, they immediately agree to participate. That is because they trust me immensely. [MHPI2]

A principal investigator said that doctors do not want to harm anyone, but pointed to a lack of understanding between doctors and the patients:

I think people get scared when they hear about research studies, but the doctor does not want to harm anyone. People are scared because of lack of education. [GJCTP18]

Thus, trust in the doctor was found to be a major reason why respondents enrolled for clinical trials. This relationship of trust between doctors and patients was perceived as unquestionable, and had a huge influence on the decision to participate in a clinical trial by a potential CTP.

A participant from Maharashtra explained the reasons for his decision to participate in a clinical trial:

My decision to participate in the trial was because free treatment would be provided to me for one year. Initially, I was very apprehensive about the cost of the medicines, since I knew that the kind of disease I have would require a very expensive treatment otherwise. Meanwhile, the doctor assured me that the new treatment was the best option I had, and also that it would cure my problem. Owing to these reasons, I agreed to participate in the trial. I believed in the doctor's assurance that the drug would cure me. [MHCTP5]

In the above narrative, the potential CTP's apprehension was allayed when the doctor "assured" him that the "new treatment" was the best option available to him and told him that it would cure his condition. While the fact of the treatment being free was a huge factor, the patient's faith and trust in the doctor was an equally strong reason. A patient seeks and accepts treatment from a doctor for a long time because she/he trusts that particular doctor. When such a doctor recommends participation in a clinical trial to a patient, it becomes hard for the patient to decline or refuse to participate.

5.2.4. Priority treatment

It is evident even to potential participants that they receive priority during the processes of a clinical trial. The absence of long queues, the lack of long waiting time, and easy access to doctors and other medical professionals are all attractive reasons that lead patients to agree to become participants of clinical trials.

This is particularly true in the case of public health care institutions, especially tertiary-level institutions, which receive large numbers of patients. Here, even if the treatment is largely free, there are other constraints, such as long waiting time and extremely limited interaction with doctors.

In such a scenario, priority treatment at the hospital combined with the attention of, and access to, doctors can be an attractive consideration or inducement for the CTP. According to him:

I am very happy with the new treatment. Since I have started taking the new drugs, my INR levels have come down to normal. I will also recommend that other patients be part of any new study as it is beneficial. Moreover, I am getting free treatment and extra attention from the hospital staff because I am enrolled in this trial. If my train is late some day or if there is some change in my schedule, the doctors and the clinical trial staff cooperate with me. Otherwise, I would have been treated like any other normal patient and would have to wait in the queue for long hours for my turn. Because of this trial I get to spend so much time with such well-known doctors, who otherwise are difficult to meet. [MHCTP5]

This is a major incentive for a patient usually struggling to get time with a doctor. However, a PI from Maharashtra explained the actual situation and dispelled some of the myths as follows:

Although this is not always true, the patients perceive that better quality of care will be provided to them if they are to be part of a clinical trial. For instance, they [believe that they] will be seen by the doctor personally. They [believe that they] can spend more time with him—get answers to all their questions—[that] basically [they will receive] higher levels of

personal care and attention than if they were to visit a doctor in his routine OPD. [MHPI3]

Availability of doctors, possession of the telephone numbers and other contact details of medical professionals, and personalised attention rarely feature in the health care system in India, particularly the public health care system. This facilitates the perception that participation in a clinical trial will ensure better and more regular medical care and attention.

A principal investigator indicated that many CTPs admitted that the reason for their participation was the expectation of better treatment in the context of a clinical trial as compared to the treatment received in an OPD. Thus, the PIs simply make participants offers that are, in the unfortunate context where participants have few options for receiving good health care, very attractive.

5.2.5. Desperation and stigma

The sense of desperation that arises when medicine has nothing more to offer, and when the only alternative available are being clinically tried and tested, was apparent in the responses of several participants. Certain medical conditions associated with high levels of social stigma, and the long suffering experienced as a result of the medical condition, created a sense of desperation amongst these individuals. This emotional state strongly influenced their decision to participate in a clinical trial, which was perceived as a feasible solution. A participant who had suffered for years from an autoimmune disorder, explained:

I have felt many times like going out to work but I do not want to go out with this disease. My neighbours treat me as if I am a leprosy patient. I am unmarried because of the problem that I am going through. I thought that nobody would probably want to marry me considering the kind of illness I have. I did not want to go through any kind of humiliation or discrimination. Anyway, who will marry me with this disease? I told my family that I will live with it on my own rather than going through any kind of marital problems. I am also not sure whether this is 'antuvyadhi' [contagious], though I know somewhere deep down that it is not. There

is a lot of stigma attached to any skin disease in our society. People are very skeptical or suspicious if they notice any symptoms and usually want to maintain a distance from those suffering from it. They think it is contagious. My mobility was restricted, as I was not comfortable going out and mixing with people. I do not attend any functions and have not seen a film in the theatre for quite some time. I keep wondering about the reasons that I am being punished by God. I don't mind going through any trial or treatment if it can help me [escape] from this dreadful disease. [APCTP2]

Another CTP who participated in a clinical trial for an HIV drug said:

Sex work and HIV both are stigmatised in our society. Being in that profession, we know what we have to go through. There is always a fear of contracting sexually transmitted disease and HIV/AIDS. We were discriminated everywhere, including at the hospitals. When I got to know that there is a trial taking place and that I can get a free check-up and treatment, I agreed to be a part of this trial. [MHCTP7]

Discussion

The reasons for participation in clinical trials are seldom singular or linear, and instead encompass a range of –economic, social, and cultural factors and influences that push and pull potential CTPs to participate in a clinical trial. In situations where treatments for their conditions are not available, or are not affordable, or are otherwise ineffective, participation in clinical trials offers the only hope for a possible recovery and cure. This may be because it provides access to a potentially useful treatment, or because it ensures that even if all else fails, the participant assumes that he/she has made an invaluable contribution through his/her participation in the search for an effective treatment or cure for the larger benefit of humankind.

These findings emphasise that the decision to participate in the clinical trial, even if an informed one, is influenced by a number of factors. The push factors can compromise the principle of “voluntariness” where the situation or the condition of the patient compels him/her to enter into a clinical trial rather than to participate in the trial as

a result of a well-thought-out and carefully considered decision. The pull factors, if they prove to be too attractive, can lead to an “inducement” to participate in a clinical trial where the benefits offered by the trial influence the decision of the patient, thereby undercutting the patient’s ability to think about the risks and benefits in a balanced or rational way.

Most CTPs decided to participate in clinical trials because of the perception of “free treatment” received through clinical trials, and also because their primary care physician had influenced their decision and had “pushed” them towards it.

When the primary caregiver is also the primary investigator/researcher in a clinical trial, patients may feel obliged to participate in the trial, perceiving a continuum of care by their doctor, which may not be available to them in the future if they were declined to be a part of the clinical trial. Studies on research participation have shown that participants’ accounts reveal complex and layered experiences overall, and also reveal blurred boundaries between patient and participant, between physician and researcher, and between treatment and research. It is important to note that when people participate in clinical trials to access treatment, contradictions arise, as CTPs view clinical trials as treatment; however, the two are not mutually exclusive, but are inextricably bound and overlapping.^{54,55}

Therapeutic misconception can arise because of many reasons, but the most important one is the reassurance given by the treating physician who is also the investigator/researcher. Even if he/she is not the investigator/researcher, he/she speaks with authority and offers assurances that the experimental drug is not risky and is better than the best available treatment, thereby unduly influencing the patient’s decision to participate in the clinical trial. Hence, the representation by the investigator/researcher of the “new treatment” as “very promising” or as “guaranteed treatment” misleads the patient into buying into the idea of participating in the clinical trial. This is a clear and deliberate violation of the code of ethics governing the conduct of clinical trials.

Free medicines are given to CTPs as a “treatment” option, but without the participants realising the risks involved and without the participants understanding that the treatment is free only because it is part of a clinical trial and that the medicine has not been tested previously.

Patients should be fully informed, and any distortions or misunderstandings that lead to perceptions that the drug under trial is the only available novel intervention should be avoided, as should the exploitation of relationships built on trust, the raising of unrealistic hopes, and the perpetuation of emotional despair and desperation when the disease is in a late stage or has no known cure. The treating doctor should not advice or influence the patient's decision to enter into a clinical trial. It is essential that an independent doctor not previously treating the patient attends to the CTP and gives honest and complete information about the clinical trial. Indeed, India's unique selling proposition (USP) is that its people do not have access to essential medical treatment and are therefore far more willing to be recruited into clinical trials than are people in developed countries such as the United States. Their inability to obtain treatment is also why they are more willing to be recruited into clinical trials. Thus, clinical trial participants in India are in need of extra protection, strengthening the argument that it is critical to highlight systemic inequities in health care delivery in the country.

Informed Consent

The advent of ethical guidelines in medical and biomedical research involving human subjects took place against the backdrop of the Second World War in the form of the Nuremberg Code (1946). Following this, in 1948, the Universal Declaration of Human Rights was adopted by the General Assembly of the United Nations.⁵⁶ With a growing patients' rights movements, and with a greater awareness of the possible risks resulting from medical research, informed consent has become a necessary prerequisite for research involving human subjects.⁵⁷ The Declaration of Helsinki provides ethical guidelines for physicians engaged in both clinical and non-clinical biomedical research, including principles for informed consent.

In the Indian context, the Indian Council of Medical Research (ICMR), in 2006, developed the 'Ethical Guidelines for Biomedical Research on Human Participants', which laid down the principles and guidelines to be followed in the consent-taking process, including components of consent and information formats.⁵⁸

6.1. Conceptual paradigm for informed consent

The right to autonomy implies that every human being of adult years and of sound mind has the right to determine what should be done to or with his/her own body. Section 13 of the Indian Contract Act, 1872 states: *Consent is when two persons agree upon the same thing in the same sense.*⁵⁹ And this meaning is also upheld by common law. The Supreme Court of India has also explained the meaning of informed consent for treatment. In *Samira Kohli v. Prabha Manchanda*, (AIR 2008 SC 1385), the Supreme Court held that doctors are authorised to do only those procedures for which express consent has been given, the only exception being the doctrine of necessity. The Supreme Court further held that doctors have to furnish adequate information to the patient to enable the patient to make a balanced judgment as to whether he/she should submit himself/herself to that particular treatment or not. This means the doctor should disclose (a) the nature and procedure of the treatment and its purpose, benefits, and effect; (b) the available alternatives, if any; (c) the adverse

consequences of refusing the treatment; and (d) an outline of the substantial risks. The patient should have the capacity to consent; the consent should be voluntary; and the consent should be on the basis of adequate information concerning the nature of the treatment procedure so that the patient knows what he/she is consenting to.⁶⁰

It is therefore essential that the person understands the procedure and grasps the risks and benefits. This necessitates communication in a language and form that the person is able to comprehend. Providing complete and accurate information to the person is the basis of the doctrine of informed consent. The person must know and agree to the risks to which he/she may be exposed.

Thus, Informed Consent in its true sense is a representation of the fundamental principles of research ethics. It implies complete respect for the autonomy and capacity of the research participant to make an informed choice. It is essential that the information provided is understood by the potential participant, and that it empowers the person to make a voluntary decision about whether or not to participate in the study.⁶¹ It is not merely a legal requirement or a document to be signed by the participant. On the contrary, it is a continuous process of communication between the researcher and the participant that is initiated prior to participation and is ongoing throughout the research study.

According to Ben Campbell:⁶²

Informed consent represents the need to respect people's autonomy. Although it is never entirely sufficient for ethical clinical research, informed consent is widely recognised as a requirement for ethical research on human subjects. Three requirements are necessary in order to obtain valid informed consent from either the participant or his or her surrogate. First, participants must be accurately informed of the purpose, methods, risks, benefits, and alternatives of research. Second, they must understand this information and how it is related to their personal clinical situation. Third, individuals must make a voluntary and uncoerced decision whether to participate.⁶³ Each of these elements is necessary to ensure that individuals freely and rationally determine that the research is consonant with their interests.

Thus, the informed consent process requires (i) assessing the capacity of the participant; (ii) providing all relevant information about the clinical trial to the participant; (iii) ensuring that the participant understands the information; (iv) ensuring that the participant makes a voluntary choice to enter the clinical trial; and (v) ensuring that the participant signs the consent form after understanding and that he/she does so voluntarily.

However, what is most important is to ensure that the underlying ethical principles of informed consent are implemented and followed during the entire duration of the clinical trial, that is, from the point at which the participant is inducted or recruited into the clinical trial to the point at which the clinical trial results are disseminated or published.

All the actors involved in the clinical trial are responsible for ensuring that the participation of the CTPs is informed and voluntary. The responsibility or duty imposed on the principal investigator and on the others involved in conducting the clinical trial is to protect the interests and rights of the participants through improved and effective methods of informed consent.

The following sections describe the process of informed consent from the perspective of participants and examine the influencing factors based on the data collected during the study.

6.2. Clinical equipoise

Clinical equipoise is the balance that the medical practitioner needs to make while giving information about probable risks, uncertainties, probable benefits while taking informed consent from the clinical trial participant. The participants should not believe or agree that one treatment is better than the other, and therefore enroll themselves in the clinical trial. There is generally a bias in favour of “new treatment” than the existing one, and the manner in which the information is provided to the participant by the doctor may also sway the decision of the participant to get enrolled in the clinical trial. Open discussion promotes trust that enhances the doctor-patient relationship and also shows respect for the patient’s right to self determination.

However, in the present study, the experiences of the participants who were enrolled in clinical trials revealed that most of the time it is the “free treatment” offered under clinical trials and the trust in the doctor that impels participants to consent. They provide consent without giving much importance to understanding the risks or the information about the uncertainties of the clinical trial and relying totally on the judgement of the doctor. Thus, clinical equipoise is not maintained.

6.3. Trust in the doctor

Trust in the doctor often also the PI, who had informed them about the clinical trial was found to be one of the major reasons for participants not paying necessary attention to the details communicated in the course of the informed consent process. Participants believed that there was no harm in the “new treatment” as they had implicit trust in the doctor. The requisites of informed consent were, therefore, not really followed by the doctor/PI. Participants gave their consent, without complete understanding, based solely on their trust in the doctor and the doctor/PI took advantage of the situation, giving the participants misleading information. One participant described how his decision to participate was largely determined by his trust in the doctor:

In the future, if I am asked to enrol in a clinical trial by the doctor, I will not hesitate, as I think the doctor knows what is best for the patient. Hence, if the doctor recommends it, then there is no harm in participating, then I will follow that. If someone else approaches me about trial participation, then I will tell him to follow the doctor's advice. If the doctor is asking you to take a certain drug or injection, then there is no harm and you must take that drug. [G]CTP11]

Another participant had a similar opinion:

I was provided with a form, which was in Gujarati. I did not read it in detail. I trust doctor sahib. I was given all the necessary phone numbers and I was asked to contact them anytime I had any complaints. [G]CTP13]

It was seen that when consent was administered by the treating doctor or even by the medical practitioner conducting the clinical trial, the participants did not put much

thought into the decision to participate in the trial, trusting the doctor's good intention.

A participant felt empowered because doctor had explained medical terms and felt obliged because doctor had done so:

I trust the doctors completely as they have done so much for us. Now I have developed an understanding about the INR levels and can also interpret the blood levels mentioned in the test reports. I thank the doctors for all this. [MHCTP5]

Other aspects of clinical equipoise are also the comfort levels of doctors in discussing complex issues and uncertainties of clinical trials. However, ethical standards should not be compromised just because they are perceived to be hard to attain. Doctor's should not feign ignorance on the best course of action or pose the clinical trial as a treatment, giving an indication of it being tried and tested. The assurance about the outcome of the clinical trial, that the drug will work is one of the factors that influences the decisions made by the participants. Similarly, information about the supposed benefits of the "new treatment" for their medical condition as explained by the doctor seemed to be incentive enough for the participants to agree to be part of the clinical trial.

One of the participants explained:

He [the doctor] explained everything about the new medicine and how it would reduce the thickness of my blood and help me with my current problem. After such a detailed explanation from the doctor, I immediately decided to be part of the study. [MHCTP5]

6.4. Understanding of the information

The cognitive processing of information provided and received on the part of the participant is determined in particular by the ability to describe the risks and benefits of the clinical trial in a manner and language that are comprehensible to the participant by the PI or doctor.

It is important to continually assess the potential participant's understanding, perception, and retention of the facts and of the information provided to him/her to ensure valid consent, especially the participant's awareness about the fact that his/her participation in a clinical trial is being sought. The recollection of having given consent might be an important measure in assessing the voluntariness of the CTP's consent, although it may not necessarily be conclusive evidence of the process of informed consent actually having taken place. Further, understanding is also the result of the interaction between the participant and the health care provider/PI taking consent, and also reflects on the quality of the disclosure made and of the capacity to give consent on the part of the participant. There are other factors that influence the consent process in a clinical trial even when the participants remember having read the consent form. As one participant from Maharashtra recalled:

Though I studied till the fifth standard, I cannot read and write. So I took my spouse with me to the hospital. There, the study coordinator explained about the study [clinical trial]. I was satisfied and decided to participate in the study. I provided a thumb impression on a form, while my partner was asked to sign [it]. I don't know what there was in that form. [MHCTP6]

In contrast to the above account, a fairly educated CTP from Maharashtra confused the consent form with some questionnaire that had been provided during the clinical trial. However, since the doctor provided a detailed explanation, the participant agreed immediately:

I think the form had some general information about health and also had some basic questions pertaining to my health. The doctor devoted a lot of time in explaining everything about the treatment. Also, I didn't see any point in reading the details about the study. I am an educated person and I know everything about the trials. [MHCTP4]

A participant from Maharashtra was not sure whether the form he signed was the consent form:

Before I was enrolled in the study, we were given one questionnaire, which had a few sets of questions related to my health. The questions

were mainly related to how I felt, [whether I had] any health issues, [whether I had experienced] any discomfort. The form was in Marathi, hence my brother-in-law read it out to me and made me understand [it]. My responses were then noted down and then both of us signed the form and gave it back to them. Apart from this, no other form was given to us. [MHCTP3]

Another participant opined:

The doctor gave me some forms, which were all in English and I didn't read them thoroughly. Moreover, I have not understood many technical terms in those forms. I just signed them and gave them back as I completely trusted the doctor. [GJCTP2]

It is clear from the above statements that CTPs often signed the consent form that they were unable to read or understand, and that this act was motivated primarily by their trust in the doctor/PI. According to some participants, they were satisfied with the explanation given by the doctor and signed the consent form without reading it. Some others were unable to recall the contents of the consent form or were not entirely certain whether the form they had signed was a consent form or some other document.

PIs also expressed difficulties in explaining the content and technical terms to the participants:

It is extremely challenging for researchers to explain the technical details to the subjects. At times, it is overwhelming and not practical. Can you tell me how the concepts of a placebo and randomisation can be understood by a subject? Even if I explain, they don't understand. [DLPI2]

A principal investigator explained his difficulties:

It is a daunting task. It is not possible to make each subject understand every detail of the study. How much understanding must be achieved in order for clinical research to proceed? [DLPI3]

A representative from a clinical research organisation suggested:

Some form of cross-questioning or check-points need to be introduced within the consent-taking procedure, which can be used to know whether the participant has understood the study or not. [CRO1]

The findings underscore the need for strengthening the process of informed consent to ensure that there is no ambiguity amongst participants with regard to consent. Clearly, in ethical and legal terms, these findings regarding informed consent reflect poorly on the current situation and the prevailing practice.

6.5. Voluntariness of consent

To evaluate voluntariness, it is important to assess that the participant is fully aware that his/her consent is for participation in a clinical trial and that such participation is purely optional. This also means ensuring that the participant is not coerced and that he/she participates voluntarily in the clinical trial, where the various aspects of such participation are not determined by the doctor or the PI alone, but are also comprehended by the participant. Assessment of voluntariness of consent becomes a complex issue when the potential CTP is ill or in a critical condition, is desperate for “treatment”, and where the offer or promise of treatment is a sufficient incentive or inducement for participation.

It may be difficult to measure voluntariness of consent when the patient is ill and in a critical condition. In addition, voluntariness of participation is questionable when substantial incentives (monetary and non-monetary) are offered for participation in the clinical trial. It appears that patients are asked to “opt out” as they are aware that they may withdraw from the clinical trial. But whether they have voluntarily “opted in” the clinical trial is an assumption that needs to be tested and verified. Informed consent is a basic right. It is about the freedom of choice, and hence ought to be respected. Ethics Committees also play an important role in protecting and ensuring that ethical considerations of obtaining informed consent for trials have been observed and followed.

However, one of the common findings was that most CTPs do not read the consent form properly. There are various reasons for not doing so. According to participants from both Andhra Pradesh and Delhi:

I was asked to sign the form, which was in Telugu and Urdu. I did not read it carefully and I don't remember the contents of the form, and I am not sure if I still have the copy of it with me. I did not understand much in it and I was also very tense. The doctor and the coordinator told me that this disease often does not have a cure and that this drug that they are going to try might help in treating this disease. [APCTP2]

I do not remember much. I was asked to sign on a form and I think it was in English. I was bit anxious at that time. [DLCTP1]

As the above accounts show, enrolling in a drug trial is a difficult decision and a cause of much anxiety to a person already suffering from a medical condition. For those who have a medical condition with no treatment, the options are limited, and this factor influences the final decision making, as can be seen above.

In a few instances, doctors and coordinators discussed matters with the family of the potential participant, explained all the options available, and helped them make a decision, as can be seen from the following narration by one of the participants:

In fact, the doctor and the coordinator spoke to my family. That really helped [us] to take a decision. He told us that this study is completely voluntary. If we do not want our child to take part, we can always discontinue and [that] this would not affect our child's normal health. [APCTP6]

“Opt in” and “opt out” in a clinical trial are indicators of how information has been given to the potential participants and of assessing the level of their voluntariness in enrolling in the trial. It is also important to understand that the autonomy of a CTP can be best ensured by providing all the relevant information through the informed consent and doing so in a manner that enables understanding by the participant.

6.6. Gender norms

Some doctors and coordinators discussed the matter with the family of the potential participants and helped them make a decision. Gender norms also came into play while assessing voluntariness when a male family member accompanied a woman, thereby influencing her consent:

During the consent-taking procedure, my husband accompanied me. They explained the consent form in detail. Most of the conversation took place between my husband and the doctor and the CRC. The consent form was in Gujarati and my husband read it. I did not read it. My husband asked a couple of questions, which were answered by the doctor and the CRC. Thereafter, on my husband's insistence, I signed the form. [GJCTP15]

Yes, he gave me a consent form. It was in Gujarati. I took it home to discuss it with my family. My husband agreed and both of us went to the hospital to sign the consent form. [GJCTP5]

Thus, the participant's husband discussed on her behalf various matters pertaining to the trial with the CRC. Here direct interaction between the doctor and the participant was limited because of the involvement of the husband of the participant and the CRC. The participant did not even read the consent form and signed it at the insistence of her husband. It is evident that deep-rooted gender norms influence the process of consent, challenging assumptions of the true "voluntariness" of the process and of the autonomy of the potential participant. PIs or recruiters have to often approach "gate keepers" of the family and be cognisant of the gender or family dynamics resulting from power asymmetry within families. Understanding these norms and the resulting dynamics is important to facilitate a process of consent that is truly informed. This is necessary to ensure that adequate efforts are made to enable the active participation of the CTPs in the consent process without foregoing their right to information and consent.

6.7. Authorisation of the informed consent

Authorisation of enrolment of participants in clinical trials was primarily done through signing/making a thumb impression on the informed consent form. However,

an ideal assessment of the authorisation would be through an examination of the informed consent process in its entirety wherein the CTP's access to complete information and his/her understanding of the many issues raised above take precedence.

Most of the participants in the study had signed the informed consent form and only a few of them remembered the process well. As one of the participants recalled:

Yes. I was satisfied with what he told me and [he] gave me the consent form, which was in Gujarati. He read out the informed consent form. I also read the form. It was around eight to ten pages long. It was also mentioned in the form that I could leave if I wished during the course of the trial. All important phone numbers were provided, and I could call at any time if I had any problem or query. I felt satisfied with what was written and signed the consent form. They also gave me a signed copy of the same. I carried it back home and discussed it with my family. They found it to be all right and gave me the go-ahead. [GJCTP2]

The involvement of a few participants in the clinical trial was very thorough, as described by one of them:

I was made to sign the informed consent form in Gujarati. The form had information about the study drug, trial duration, doctor's name and details of benefits and risks. I was given a signed and dated copy of the form. The form also stated that there was an option to withdraw from the study at any point of time. The doctor also explained about the study drug, free lab test, duration, frequency of visits, activities, side effects, and appropriate medical care. [GJCTP8]

However, some participants signed the form despite not understanding the contents and without seeking clarification of their doubts:

I signed the form. It was in English, I have not understood much. They gave me a copy of the form. [MHCTP9]

Although the CTPs signed the consent form, indicating their willingness to participate in the clinical trial, this was not tantamount to their giving informed consent as is legally mandated because this authorisation was not always indicative of true understanding, voluntariness, and consent.

6.8. General measures

The satisfaction of the participants with regard to the process of informed consent is a measure of whether informed consent has been implemented appropriately. Others who have been involved in the informed consent process, such as the spouse, offspring, other relatives, or those who have an influence on the participant, may also provide important insights and perceptions. The rate of participation in a clinical trial should not be considered the only measure of success because, for example, if the risks are downplayed, voluntariness is undermined. There are also other potential gaps in the process that would affect the assessment of informed consent and participation in clinical trials.

The role of the person accompanying the patient is also important. The patients discuss the possibility of taking part in the clinical trial with the person accompanying them. Many participants told that the person accompanying them to the hospital helps them get their doubts clarified. Experience of one of the participants with her sister highlights this point:

They gave me a form that was in Telugu. The coordinator read the form to me and asked me to sign it. My sister was with me too. She also spoke to the doctor. We were convinced and I agreed to participate in the trial and it was solely my decision. It was not forced by anybody else on me.... The doctor and the coordinator gave their phone numbers to me, so that in case of any problem I can get back to them. They were very friendly.
[APCTP5]

Many participants took the forms home to discuss it with their family members. The participants are particularly vulnerable when they are alone and when have to take decision on their own. Another participant from Gujarat had similar situation to be narrated:

When they gave me the form, I was on my own. There was no one with me. They told me that I could take it and discuss it with my family and bring it back. But it would have been difficult for me to take the form back home and then come back here to return it. [GJCTP17]

6.9. Patterns of consent taking

The consent-taking process from the point of view of the key informants reflects certain shifts in articulation and language. The general pattern of the consent-taking process is described by a CRC as follows:

The PI speaks to the patients about the clinical trial and gives them all the details. The doctor introduces the study to the subjects and discusses the consent taking process with them. Then if they are willing to be part of the trial, the patients are referred to the clinical research unit to be part of the trial. The IC formats are then explained in detail and the process of consent is completed. One copy is provided to them and another is kept with the PI. [DLCRC1]

According to another PI in Delhi:

At the institute, there is a separate Research Coordinator who sits with the patient and explains the entire protocol of the clinical trial. If the patient shows interest in becoming a subject then we send him to the Research Coordinator. The patient can clear all his doubts about the study with the help of the Research coordinator. Once the patient is convinced about the study, he will go through the informed consent form. ...the patient has to go through it and then sign. The research coordinator at the institute is responsible for taking informed consent from the subjects. [DLP12]

Another PI opined:

One copy of [the] ICF is provided to the patient in the language he requests and the other copy is kept with the PI. After all this, the patient is provided with enough time to think and discuss the trial with his family. Once he agrees verbally, then he is asked to sign the informed consent

form. The PI and the Co-PI of the study also sign the informed consent form. The patient can also ask any questions he wants to, and it is the PI's and/or the Co-PI's responsibility to answer them truthfully and satisfactorily. [APP15]

The above description by the PI, while idealistic, is not in consonance with the perspectives and concerns of the CTPs as discussed in this chapter. As seen in the section on the perspectives of the participants, one of the important factors in the informed consent process is the person who administers the consent. As per the above description, in some instances the PI administers the consent, and in others it is the research coordinators who are responsible for it. One of the EC members points out that informed consent is administered mainly by the CRCs rather than the PIs for the following reasons:

I am sure that patients are not well informed about the trial, as the PIs do not have sufficient time to spend with the patients. So they depute coordinators, who are not experts to monitor or conduct trials. PIs should be responsible for checking the ethical part of the trials. [EC1]

Another EC member raised doubts about the content of the form:

Even some of the informed consent documents are inadequate in providing details such as foreseeable risks, description of the procedures, benefits to the subject, and so on. I raise these issues when the protocols come to me. [EC2]

Here it is important to understand the regulatory requirements related to the informed consent. Schedule Y of the Drugs and Cosmetics Act (1940) provides a checklist of essential elements to be included in the participant's informed consent document, which includes a description of the procedures to be followed, reasonably foreseeable risks to the participant, benefits to the participant, specific appropriate alternative procedures or therapies available to the participant. Very few participants and KIs mentioned all these factors.

An EC member offered the following opinion about the attitude of PIs towards informed consent:

Pls know very well that informed consent is not really a piece of paper and [that] it is a legal entity. Still, they take it very casually. One should follow what was laid down in Schedule Y and in the ICMR guidelines. They are very important, though not many follow them. [EC1]

A CRO representative highlighted concerns regarding the length of the informed consent form, which can itself act as a barrier to understanding:

The length of the form is intimidating for the patient. From the number of pages to the level of details, it is overwhelming for subjects. I find them very complex, and it gets very difficult to explain all these pages and information in an OPD setup. [CRO1]

Another CRO representative was also of the opinion that the size or length of the informed consent form should be reduced and that it should be made more readable and easier to comprehend:

The informed consent form in itself is a cumbersome document. The sponsors, in order to safeguard themselves against any liability, put everything down, and as a result the consent form is spread across 17–18 pages. For any healthy person, to read such a long document in detail is tedious, and for a patient it would mean a Herculean task. I suggest that a consent form should not be more than two pages and should be tested using [a] readability system as is done in the US or the UK. [CRO2]

The length of the consent form—being either too short or too long—raises many issues. Both instances can lead to ambiguities for the CTPs. A lengthy consent form is just a means of “playing safe” for actors involved in the conduct of clinical trials, where the attempt is to preempt all issues and objections in order to reduce their own liability.

A sponsor, when asked about the process of informed consent and the prevalent unethical practices, said:

In clinical research, another thing that the media or [the] public forgets to understand is that everything does not end with the sponsor.

The sponsor can, at best, provide an IC document, provide all the approvals, and the framework of the trial to the investigator. Beyond that the sponsor is not expected to be a part of the IC process or of the screening of the patients. That is left to the investigator. [SP]

He also projected the role of the sponsor as a facilitator rather than as someone who actually conducts the study or as someone who is ultimately responsible for any unethical practices in clinical trials. He further elaborated:

There is no mechanism by which a sponsor will be able to find out whether an investigator has really given a proper informed consent because in front of us is a document which is signed. For illiterate patients, we accept a thumb impression, with a legal representative's signature, or an impartial witness is called. Generally, what happens is [that] in the media, people often claim that they did not know they were participating in a trial. When you show them the form, they feign ignorance, [and] claim they did not know they were signing a consent form. Who do you believe? Unfortunately, the sponsor cannot take responsibility for this. [SP]

The sponsor reaffirmed that at present, there is no system to assess whether the participants have comprehended the information in the consent form.

6.10. Methods of taking informed consent and their effectiveness

The profile of the CTPs is diverse and in case of non-literate participants, alternative methods of obtaining informed consent, such as witnessed consent using a third party should be used. Similarly, there are various innovations in the methods of taking informed consent and in the ways of recording the effectiveness of the procedure of informed consent. Experts have suggested simplifying the process by using language that is easily understood by the participants and recording the process, both through writing and through video documentation.

With regard to the video recording of the process, one participant said:

I am not personally concerned about audio-video recording, but feel that people may not easily agree with such consent [taking] procedures. They

may want to maintain their confidential status and stay aloof. I feel that directly talking [to them] will be better than [making] a documentary or [an] audio-video explanation of trials. [GJCTP19]

A sponsor however endorsed the idea of video recording of the consent process. He said:

We have been successively suggesting to the government that we [should] incorporate a process through which it is possible to film the entire consent-taking process. The patient can be masked. Keep the patient's identity confidential, etc. At least, it will ensure that it is not the case of one person's word against the others. [SP]

However, one of the PIs disagreed with the assumption that video-recording of the consent process is a good idea:

Consent need not be video recorded. These are very private matters and need not be put up in the public domain. People may not like to be taped and would rather speak to the doctors personally. [GJPI1]

A participant questioned the usefulness of video recording of the informed consent process:

How is it going to help us? Will they give us a copy? Even if they give us [a copy], where are we going to watch [it]? We don't even have [the] facilities [to watch it]. [GJCTP14]

Participants from vulnerable communities—sex workers and PLHIV—were concerned about issues of privacy and confidentiality:

We don't want to be visible and subject ourselves to any harassment in the future by [the] police or anyone [else]. [DLCTP1]

Similar issues were also raised during a group discussion where a PLHIV expressed their concerns about protecting their identity and privacy in case they were video-graphed. The use of such methods to document and record the process of consent needs to be further discussed in order to gain a proper understanding of the

implications of these actions, whereby potential participants from certain communities that are stigmatised are reluctant to be video-graphed.

Discussion

The interviews with the participants reveal that they are passive participants with regard to informed consent, with negligible spaces being available to them for exercising their agency to seek clarifications or to ask questions about the clinical trial and their role and participation in it.

Thus, the interviews with the CTPs and the KIs emphasised the fact that informed consent is not merely a single event, limited to the signing of the consent form by the participant. Rather, it is a process initiated by the PI while appraising the potential participant about the clinical trial and extends till the conclusion of the trial. It is important to foreground the principle of consent and to extend it to the final dissemination of the clinical trial data as well as the use of the data for any other purpose. This makes re-consent necessary, i.e., the taking of consent again from the CTP for the authorisation of the use of the data generated. Hence, the principles of informed consent transcend all the activities of the clinical trial where the participant and his/her clinical data are concerned.

The decision to give informed consent and to participate in a clinical trial is influenced by a number of factors such as the socio-economic status of the participant; the medical condition of the potential CTP; the availability of, and access to, any alternative treatment; the way in which the research team explains the study; and the manner of the person who administers the consent process/form. Open discussion respects the participant's autonomy and his/her right to self-determination. It is also equally important to examine if the underlying ethical principles of informed consent are truly followed or implemented on the ground during the entire duration of the clinical trial, i.e., from the point of recruiting patients to the point when the clinical trial results are disseminated or published.

In the present study, the interviews with CTPs revealed that often it is the free treatment offered as part of the clinical trial and the trust reposed by CTPs in the doctor that impels them to participate in the clinical trial. These factors lead

participants to sign consent forms without necessarily understanding the risks or comprehending the information about the uncertainties of the clinical trial. Thus, participation is not determined by the self, but is based on reliance on the doctor's judgement, resulting in compromise of clinical equipoise.

The information provided to the participants seemed to significantly influence their decision to participate in a clinical trial. The CTPs' anxieties were allayed by the assurances given by the PI or the doctor that there would be no risks. The CTPs may not be adequately informed about the risks and/or benefits, nor may they have the means or the power to demand compensation for any adverse health outcomes that may result from participation in the clinical trial. Obtaining consent under such circumstances, as a result of the undue influence of the PI or the doctor, cannot be considered as consent in the true sense. This, in fact, amounts to serious negligence and breach of trust.

The new amendments to the Drugs and Cosmetics Act, 1940, have also made it mandatory for the investigator to 'hand over a copy of the patient information sheet and [the] duly filled Informed Consent Form (ICF) to the trial participant or [to] his/her attendant'.⁶⁴

The process of informed consent for participation in clinical trials must adhere to the provisions of the existing protocols, both legally and ethically. Any non-adherence—such as the failure of the participant to have understood the information contained in the form, or the participant being given no choice in the matter other than having to sign the form, or equating the clinical trial to "treatment" towards getting the participant's consent—would be tantamount to no consent having been given by the potential participant. Such a clinical trial would be in complete violation of the provisions of the Drugs and Cosmetics Act, 1940. Respect for participants and regard for their autonomy must be maintained at all times.

The asking of questions by CTPs does not necessarily indicate the giving of informed consent on their part. All the information required for the securing of informed consent should be provided to the participants, including details about the probable short-term and long-term risks, benefits, alternatives, and treatment regimes. Details about the compensation (in case of any injury) and the insurance to be paid by the

sponsor through the PI or any other agency should also be included in the consent form. Their right to withdraw from the clinical trial at any time must be clearly communicated to them and to their families.

Recently, on 19 November 2013, the Drugs Technical Advisory Board (DTAB), with the approval of the Ministry of Health and Family Welfare (MoHFW), has recommended the amendment of Schedule Y.⁶⁵

In all clinical trials, in addition to the requirement of obtaining written informed consent, audio-visual recording of the informed consent process of each trial subject, including the procedure of providing information to the subject and his/her understanding of such consent, is required to be done while adhering to the principles of confidentiality. Such audio-visual recording and related documentation would be preserved. This is applicable to the new subjects to be enrolled in all clinical trials including Global Clinical Trials.

All the Sponsors/Investigators/Organisations and other stakeholders involved in [the] conduct of clinical trials in the country are hereby directed to adhere to the above requirement of [the] audio-visual recording of [the] informed consent process of trial subjects with immediate effect.⁶⁶

Video recording of the procedure of informed consent needs further deliberation and also requires the incorporation of the CTPs' concerns. The need for maintaining confidentiality and ensuring that video recordings are not tampered with or manipulated in any way are important concerns that have been expressed by some respondents. Similarly, the claim of audio-visual recording being a foolproof method of ensuring "informed consent" needs further examination and discussion. Concerns about the violation of privacy of participants are real, necessitating clearly defined norms for the storage and use of video-taped consent processes to ensure that they are not misused. The wish of any participant who had given consent to video-taping on the express condition that his/her identity would not be exposed must be respected.

It is necessary to explore and adopt other methods of taking informed consent, and of ensuring that the rights of CTPs are protected and enhanced. Facilitating access to information and carrying out a public education campaign about research and clinical trials in order to have a better informed population is necessary.

Standard Operating Procedures (SOPs) should be developed for the conduct of clinical trials in general, but also specifically for the process of consent, and must include all the relevant details about the verification of the consent procedure, i.e., who, when, where, how, and why.

The findings of this study bring to the fore the ground reality that informed consent is rarely implemented in its true sense. The focus continues to be largely on creating written records or documents for the benefit of those conducting the clinical trials, rather than ensuring that the principles of informed consent are operationalised. Doctors, PIs, CRCs, ECs, and sponsors have a key role to play in ensuring that informed consent is implemented in a robust, ethical manner, so that the capacities of participants to understand the implications of the “*same thing in the same sense*” are enhanced, and to ensure voluntary consent, without any kind of undue influence, misrepresentation, and misinformation about the clinical trial. Informed consent continues to be implemented in a limited manner, thereby compromising the protection of the rights of the clinical trial participants.

Adverse Events and Compensation

This chapter explores the reporting of adverse events and experiences of clinical trial participants with adverse events (AEs) and the participants' understanding of compensation for any injury sustained during a clinical trial and the recent developments in the context of regulations and new amendments in Schedule Y of the Drugs and Cosmetics (Third Amendment) Rules, 2013, regarding compensation and serious adverse events (SAEs) during clinical trials.

7.1. Adverse events and serious adverse events

Risk of injury is inherent in any biomedical research study on human participants. The injury could be in the form of direct or indirect physical, psychological, social, or economic harm, and may require only acute or emergency care or long-term medical care. The issue of providing compensation for research-related injury has been a matter of some debate in the world of clinical research.^{67 68} While conducting clinical trials, a key component of the procedure is recognising and reporting AEs⁶⁹ and SAEs.⁷⁰

In developing a new drug, device, biologic or vaccine, the safety of the product or procedure being investigated needs to be determined through the collection and analysis of data related to the AEs as reported and recognised. Many clinical trial studies in India in the past had raised concerns over the reporting of AEs or SAEs. There is a lot of ambiguity and lack of clarity in the reporting of AEs or SAEs even in the present context.

Certain AEs are known or anticipated based on what is known about the trial drug. This knowledge could be based on information about similar drugs that have been tested, or on the outcomes of similar trials that have taken place earlier. The investigator's brochure should have all the information about AEs. Further, potential AEs or SAEs are also detected by physically examining the clinical trial participant for these events. Any abnormality needs to be investigated further.

7.1.1. Information given to clinical trial participants about adverse events

Some of the clinical trial participants were given a list of adverse effects such as cold, cough, fever, dizziness, pain, and, in some cases, the phone numbers of doctors and CROs were given so that the participants could contact the doctors immediately on the occurrence of AEs. According to a participant:

During the trial, they asked me to report if there was any pain, fever, headache, or any other problem immediately. The doctor explained me that sometimes during the initial doses one may suffer from dizziness or suffer from a mild fever. [GJCTP12]

Most CTPs reported that information brochures were not given, nor did they undergo regular medical examination. They were just asked to report if they experienced any AE. Most PIs stated that they list the plausible side-effects and explain these in detail to the participants. However, some PIs said that they just give an overview of the process that the participants need to follow when they experience AEs. The PIs said:

I explain to the participants about the side-effects, the known adverse events, SAEs, etc. Also, we do not know if any new AE/ SAE will arise in the future or not; this aspect is also explained to them. [GJPI3]

During the [informed] consent process, the team explained to the parents that if the child experiences any side-effect, including fever, they should immediately inform the Co-PI and the CRC. It is very important to record all the adverse events during the trial period. [APPI5]

A CRC elaborated the process of monitoring the AEs:

The clinical research unit team is in-charge of monitoring the subjects through his monthly visits in which we check for drug compliance and if there are any adverse events, they are documented. ...Also at the same time, we tell all the subjects that they should immediately contact us, if there is any problem, even if it is a cold, cough, etc. they should let us know. [DLCRC1]

However, the responses of the PIs on this issue revealed a clash of interests. Recognising the importance of informing the prospective participants about AEs, a CRC from Gujarat subtly indicated that informing the participant about AEs in detail might scare them away. According to him:

It is important for the patients to understand what the possible side-effects are. Just because any other person in the clinical trial has not suffered from any adverse effects does not mean that he or she will also not experience them. At the same time, we also need not place too much emphasis on death as an adverse effect, as this would scare away any individual. [G]CRC1]

This again not only raises questions about the informed consent process, but also raises serious doubts about those conducting clinical trials upholding the rights of the participants.

As part of the procedure for preparing participants for AEs, they were also informed about the process that should be followed in case of occurrence of any such event. For this purpose, the contact numbers of the members of the clinical trial team were also shared with the participants. According to a PI from Andhra Pradesh:

All the subjects' parents were given three phone numbers [those of the PI, Co-PI, and CRC] so that they can contact any of them for any problem. We are not doing any charity for the patients, and it is our job as investigators to inform the parents about adverse events and also [about the] reporting of AEs. [APPI5]

The CTPs were expected to identify the AEs themselves and report these to the doctor. Some participants said:

No, he [the doctor] didn't inform me about the side-effects or the procedure to be followed in case I experience any side-effects. The doctors told me not to take any other treatment for this stomach problem and in case I took medicines for any other ailments or get admitted in the hospital, I should inform them immediately. During the clinical trial, I also had to observe several dietary restrictions. [MHCTP1]

I was given all the necessary phone numbers and I was asked to contact them anytime I had any complaints. [GJCTP13]

As a next step, in case of occurrence of any AE, the KIs reported providing immediate medical attention to the participant. According to the CRCs from Andhra Pradesh and Delhi:

And in case any hospitalisation is required or if immediate treatment is needed, the hospital will provide [this] immediately. [APCRC1]

In the case of any adverse events, if someone comes to the hospital, they will be provided the necessary treatment. They are expected to pay some deposit by the hospital prior to hospitalisation, which is reimbursed later. But even if they do not have the money, the PI intervenes and ensures that there is no delay in getting the patient admitted in the hospital. [DLCRC1]

7.1.2. Adverse events experienced by clinical trial participants

Some participants experienced dizziness, fever, headache, pain in the chest, and severe dryness of the skin, etc. These were reported by the participants to the doctors, who attended to the problem. According to one CTP from Gujarat:

I usually feel dizzy when I take an injection. The doctor asks me to rest for 15–20 minutes and I feel better after that. I came to the hospital three days back. I was admitted here and today I am being discharged from the hospital. I went back and I had pain in my chest for some time, so my son called the hospital. They told me to come here immediately and get admitted. But I told them I would come after a few days as I was not feeling well enough to travel. [GJCTP17]

A mother whose child was a part of a vaccine trial said:

After taking the teeka, my child had fever. I knew that usually after such vaccination, children sometimes get fever, so I was not very worried. [APCTP6]

Various AEs were witnessed by the PIs, CRCs and their management during different clinical trials:

One woman had myalgia but she was treated at the OPD. [APPI1]

Of course, a few children who were vaccinated had fever following the administration and they were treated with Crocin. [APCRC2]

Headache, dizziness sometimes stomach pain were reported by the subjects. [GJCRC2]

7.1.3. Reporting of adverse events

Speaking about the reporting of AEs/SAEs to the sponsor and to the members of the EC, a CRC from Gujarat said:

In case of adverse events, we have to notify the sponsor; this depends on the severity of the adverse effect. For example, if a headache persists over a long period of time, we have to report the AE/SAE to the sponsor as well as the Ethics Committee within 24 hours. The assessment of the AE is done by the PI and the Co-PI, and if it is found that the AE caused is related to the trial drug, then sometimes, in cases of global studies, even the global team is present to assist the PI and the Co-PI. [GJCRC2]

Speaking along similar lines, PIs from different states said:

In case any of the participants experience a side-effect, or what we call an adverse event, the PI first has to inform the Ethics Committee and the sponsor. The sponsor, in turn, will inform the DCGI. Then, depending on the causality, the sponsor may also inform the other sites. The Ethics Committee may also question the PI and, if it is felt that the trial is unsafe, they may decide to call off the trial completely. So far, we have had no such instance. [MHPI3]

Any AE has to be reported within 24 hours of its occurrence to the sponsor. [APPI2]

All AEs are managed efficiently by my team at the hospital and as per the protocols we inform the EC and the sponsor about the AE and SAE within 24 hours. [GPI1]

Contrary to these general responses received a PI from Andhra Pradesh felt that it was not necessary to report AEs to the regulatory authorities and to the EC:

I have not experienced such an incident as yet. But I have been told that in such cases, the patient is to be admitted and treated accordingly, following which the sponsor is to be informed. Every visit of the patient is also recorded and [the information is] sent to the CRO and the sponsor accordingly. The EC and the DCGI need not be informed. [APPI3]

However, variations existed among the KIs about the time duration within which AEs should be reported to the DCGI. Some KIs said that the AE should be reported to the EC members and the DCGI within 24 hours of its occurrence, while other KIs said that the duration should be between seven and 14 days:

The information is also shared with the CRO and also with the IEC. And within 14 days the sponsor reports the matter to the DCGI. [APCRC1]

After the discovery of any injury or death related to a clinical trial, the sponsors should inform the DCGI within 24 hours. [DLCRC1]

Explaining the process to be followed in the case of reporting of AEs, a PI from Maharashtra said:

In case any of the participants experience a side-effect, or what we call an adverse event, the PI first has to inform the Ethics Committee and the sponsor. The sponsor, in turn, will inform the DCGI. Then, depending on the causality, the sponsor may also inform the other sites. The Ethics Committee may also question the PI, and if it is felt that the trial is unsafe, they may decide to call off the trial completely. So far, we have had no such instance. [MHPI3]

7.1.4. Non reporting of adverse events

Although protocols may be in place for AE management, many a times the AEs are not reported adequately by the PIs because they expect that the participants should

report them. Sometimes the participant goes to a local doctor for treatment and does not report the AE to the PI. It therefore appears that the PIs do not conduct a regular check-up nor do they follow up to report or document the AE and SAE. One of the PIs explained:

Sometimes subjects who get sick, they just go to a local doctor. In such cases, we cannot do anything about it. We tell them to come back only to us. [DLPI3]

Speaking along similar lines, another PI from Maharashtra said that sometimes when a patient visits a local doctor, the AE might completely go unrecorded, and the expenses incurred by the participant while availing the treatment from the local doctor are also not reimbursed. He opined:

Sometimes in case of an emergency, the subjects may visit a nearby doctor. In such cases, the PI would only come to know about the emergency or the occurrence of a side-effect at the next visit. There may also be cases where the subject does not inform the PI of such an event and it may go completely unrecorded. In such cases, where the subject seeks treatment for any side-effect at an external facility, the amount spent is not reimbursed. However, our Ethics Committee is discussing this issue and we are trying to set up a mechanism through which such cases can be minimised. [MHPI1]

7.1.5. Impact of improper and irregular recording of adverse events

The reporting of AE and SAE is very important, and following up with the participant on a regular basis would help in the process of recording the same, in identifying and handling the AEs, and in making linkages between the AEs and the clinical trial in a logical and scientific manner. It is essential to assess the safety of the trial drug and to ensure that the reporting is done regularly in a detailed manner. It appears that AEs are recorded primarily to give a report to the sponsor, the EC, the DCGI, etc. It has been seen that the vast majority of the AEs are recorded as unrelated to the clinical trial and therefore no compensation is provided.

The Government of India (GoI) has compiled the number of deaths that have occurred during the clinical trials since 2005 in the country.⁷¹

Table 7.1.5

Year	Total SAEs of Deaths	Deaths related to clinical trials
2005	128	5
2006	137	2
2007	136	4
2008	288	8
2009	637	16
2010	668	22
2011	438	16
2012	436	16

[Source: Clinical Trials in India (30.8.2013) Link: <http://mohfw.nic.in/index1.php?linkid=338&level=1&lid=1640&clang=1>]

As can be observed from the table, a miniscule number of deaths were recorded as being related to clinical trials, with only about 4 per cent in 2005, 1.4 per cent in 2006, about 2.5 per cent in 2009, and 3.6 per cent in 2012, whereas the vast majority of deaths that occur during or after clinical trials are linked to some other cause, such as chronic diseases such as cancer, cardiovascular conditions like congestive heart failure/ stroke, and other serious diseases, etc. This makes a case for closer examination of the SAEs of death as some of them are categorised as “probable”.

7.1.6. Recent developments

In January 2013, DCGI amended the Drugs and Cosmetics Act (DCA) 1945 and brought in the following Notification on SAEs. As per the Notification GSR 53(E), the following guidelines are to be followed in the instance of adverse and serious adverse events:

Serious Adverse Events (SAEs) [5(A)]

- (1) A serious adverse event is an untoward medical occurrence during clinical trial that is associated with death, in patient hospitalization (in case the study was being conducted on out- patient), prolongation of hospitalization (in case the study was being conducted on in- patient), persistent or significantly disability or incapacity, a congenital anomaly or birth defect or is otherwise life threatening.
- (2) The investigator shall report all serious and unexpected adverse events to the Licensing Authority as defined under clause (b) of rule 21, the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial, and the Ethics Committee that accorded approval to the study protocol, within twenty four hours of their occurrence as per Appendix XI, and the said Licensing Authority shall determine the cause of injury or death as per the procedure prescribed under Appendix XII and pass orders as deemed necessary.

Source: Gazette of India, Ministry of Health and Family Welfare (Department of Health), Notification GSR 53(E), New Delhi, 30th January, 2013.

In addition to reporting of AEs and SAEs, all health care facilities and institutions that are involved in conduct of clinical trials must ensure necessary infrastructure and health care in case of such events. Health care professionals in these facilities and institutions should be oriented prior to the commencement of the clinical trials, so that requisite preparedness and health care can be provided without delay.

Discussion

It is evident that most of the participants were not fully informed about the possible side effects and risks involved in participating in clinical trials at the time of recruitment. In a few of the cases, in addition to the regular follow up participants were instructed to report to the CRC or PI in situation of any AE.

When AEs are not reported the safety data of the experimental drug is actually forged, which raises grave concerns about the safety of the drug once it enters the market. Apart from the safety of clinical trial participants and future users of the drug, this may also threaten the reputation of the pharmaceutical company marketing the drug.

It will always be difficult for the CTPs or their family to prove that the deterioration of the health of the participant, or the AE or the SAE or death occurred primarily due to the drugs under trial. This is because the causation of the AE or SAE or even cause of death is assessed and recorded only by the PI, who may not want it linked to the clinical trial, given his/her personal interest and possible gain that may result from a favourable clinical trial result. He/she could very easily attribute the cause of death or adverse event to natural causes or natural progression of the disease, especially in the case of ill or severely ill patients with no available treatment.

It may not be obvious that the patient fared worse as clinical trial participants than they would have in the absence of the research intervention. It can always be argued that the patient died of natural causes and the same cannot be attributed to the action or inaction of the clinical trial. Such circumstances will make it extremely difficult for clinical trial participants or their families to claim compensation.

The PI is responsible for reporting the AEs as he/she has the role of primary care giver to the patient. It is important that the participants be assessed by a doctor independently before the clinical trial commences and at regular intervals after the commencement of the trial, and should record the effect on the patient independently. This could help clinical trial participants to have an unbiased opinion on the AE or SAE or cause of death, that could help them challenge the claims of the sponsor, PI and other agencies.

It is also important that the participants are given a copy of their medical records taken by the PI prior to, during and after the clinical trial; all test reports and documents with regard to their medical condition, hospitalisation, number of doses given, etc., should be given to the participants of the clinical trial, as a record for them to be able to obtain not just a second opinion, but also to seek compensation. Towards protecting and promoting the right to health and life of all clinical trial participants, the presumption that an AE or SAE or death has occurred as a consequence of the vaccine or drug being tried on them, is fair and justified and must be ensured through requisite guidelines and legislation.

7.2. Compensation

In general, all possible precautions should be taken to minimise risk to clinical trial participants. However, in case the clinical trial process leads to injury or death, compensation to those participants, who are subjected to or sustain trial-related injury or death, is essential. Compensation is defined in the Oxford dictionary as the process of providing, ‘*something, typically money, awarded to someone in recognition of loss, suffering or injury*’.⁷²

In the context of clinical trials, the AEs can range from relatively minor harm to major injuries (temporary disabilities) or even disastrous injuries (leading to permanent disability or even death).⁷³ In India, from 2005 to 2012, 89 deaths of participants were reported as being “related to clinical trials” out of the SAEs of total deaths of 2,868 participants. Compensation was given in 82 cases, whereas compensation was not paid to seven cases. The year-wise details are as follows:⁷⁴

Table 7.2.a.

Year	SAEs of Death	Deaths Related to Clinical Trials	Compensation Paid
2005	128	5	5
2006	137	2	0
2007	136	4	4
2008	288	8	7
2009	637	16	13
2010	668	22	21
2011	438	16	16
2012	436	16	16
Total	2868	89	82

Jesani (2013) has argued that for the few cases reported by the sponsors as related to the trial, there were many times more deaths under the categories such as “possible”, “suspected”, etc., which should have been investigated by the Central Drugs Standard Control Organisation (CDSCO). Such investigations never took place. Thus, it is

possible that there might have been many more cases which were entitled to compensation but did not receive any.⁷⁵

The issue of compensation for AEs during clinical trials was being debated when the interviews for this study were being conducted in 2011-12. There were many ambiguities in terms of determining who should be given compensation and what should be the quantum of the compensation. These ambiguities still persist. In January - February 2013, amendments were made to the Schedule Y of the Drugs and Cosmetics Act rules, addressing some of the issues that were being consistently raised by concerned members of the civil society. However, many issues with respect to compensation still remain unaddressed even after these amendments.

With this background of debate on compensation and changes in the regulatory directives for compensation in 2013, the rest of the chapter is presented in three sections. The first section discusses the perspectives of the key informants as recorded before the amendments to the Schedule Y in January-February 2013. The second section presents an overview of the current guidelines on compensation for clinical trial participants in case of SAEs of death during the clinical trial. The third section highlights the concerns regarding these amendments in the context of compensation.

7.2.1. Perspectives of the key informants⁷⁶

The key informants raised many issues regarding compensation to the clinical trial participant in case of the SAEs in clinical trials. However, the concerns discussed by the KIs are presented here in order to give a background of the issues and concerns that were being debated before amendments took place, and many of them still need further improvements and fine tuning.

The key informants largely agreed that compensation should be provided to CTPs in case of serious adverse events. As one of the principal investigators said:

I totally agree that there should be compensation paid to any trial-related injury and death irrespective of causality, with the sponsor taking the responsibility. [APPI2]

Even though most key informants agreed that compensation should be paid, the contentious issue was whether compensation should be paid to terminally ill participants and what the amount of compensation for them should be.

It [compensation] is a complex issue when it comes to oncology trials when you know that the patient is terminally ill. It is also important to understand that most oncology patients are also at an advanced stage [of the disease] and death is inevitable. How can we decide that death was due to the trial drug when the subject was terminally ill and was in an advanced stage of cancer? This needs some debate and discussion, I suppose. [APPI2]

Key Informants differed about the authority that is empowered to decide whether to give compensation, and if so, what the quantum of compensation should be. A clinical research coordinator from Gujarat stated that the amount of compensation is decided both by the sponsor and the PI. In his words:

Usually, the sponsor decides the amount of compensation. However, it is the PI who assess the circumstances and calculate the amount accordingly... The compensation is usually decided by the Ethics Committee and [the decision is] then forwarded to the DCGI. Now there are some changes in the policy with regard to compensation, and there is a new understanding about the establishment of causality, which has been expanded. The ultimate decision regarding compensation is to be taken by the DCGI. This has caused problems for [the] conduct of trials. [GJCRC1]

Thus, CRC refers to different stakeholders who decide the compensation. Later the CRC referred to the recent changes in the regulatory framework regarding compensation. The CRC felt that these new changes are causing problems for conduct of trials. A program manager from Gujarat explained the process they followed about compensation:

Earlier it was the PI's decision to arrive at the quantum of compensation to be paid to the trial participant. However, now the EC members are

discussing the best practices for doing this. If there is a death, the EC will decide on the compensation. In case of hospitalization, the reimbursement will be as per actual expenditures. [GJPM]

A few of the key informants also pointed out that sometimes the sponsors and PIs differed on the issue of compensation. The compensation was not calculated uniformly. One of the sponsors expressed the need for uniform scientific methods to calculate the compensation. The key informants supported the new developments and felt that these developments will remove ambiguities.

It is clear from the above narratives of the key informants that there was confusion and an inconsistent manner of handling the issue of compensation. While on the other side, very few participants mentioned compensation during the interview. It was observed that the participants were not aware of the compensation in case of occurrence of AEs or SAEs. Even those who had mentioned reading the consent form and had indicated that they were satisfied with the information provided in the form, were unable to recall any mention of compensation. A few participants mentioned receiving travel reimbursement when asked about compensation. A participant from Andhra Pradesh recalled:

I don't think there is any mention of insurance or compensation in the [consent] form....I did not give too much importance to the contents of the form. [APCTP1]

From above section, it can be seen that on one side, there was substantial confusion and disagreements among the key informants in the way compensation should be handled. On the other hand, the participants were largely unaware of compensation. Keeping this background in mind, the following section briefly presents the amendments that were made to the Schedule Y of Drug and Cosmetic Act in January-February 2013.

7.2.2. Overview of the current guidelines for the compensation

Owing to the pressure on government to address the issue of compensation in clinical trials, Schedule Y of Drugs and Cosmetics Rules was amended in January, 2013 in

order to specify the procedure for processing of reports of SAEs including deaths occurring during clinical trial. After amendments to Schedule Y on compensation, a formula to determine the quantum of compensation, in case of death, to be paid by the sponsor to the participant has been uploaded on CDSCO website.⁷⁷

These amendments represent a definite advance in the ethical standards in India for two reasons; firstly because it holds the sponsor completely accountable for the free and complete medical management of all the SAEs and secondly, it recognises that all participants in the clinical trial should be considered for compensation in case of SAEs and not only those being given the experimental drug.⁷⁸ To address the issue of quantum of the compensation, three independent expert committees were constituted under the chairmanship of Dr. A. K. Agarwal to determine the formula for quantum of compensation to be paid by the sponsors. Considering three factors namely age, risk and base amount, the following formula was devised for calculation of the quantum of the compensation in case of the deaths related to clinical trials.

There is now a guiding formula, which can be used uniformly across the country for the computation of the compensation. However, there are many issues that remain to be addressed even after these amendments. The amendments themselves raise some new concerns. These issues and concerns are discussed in the following section.

7.2.3. Concerns regarding the current framework on compensation

The new amendments and the formula in their current form raise the following concerns:

- These guidelines only cover serious adverse events resulting in death. These guidelines are silent about those that do not result in death.
- The formula is not clear about the compensation in case of death of children below 16 years of age.
- Currently, there is no system for appeal for aggrieved participants and families in case of disagreement among clinical trial participants in matters related to compensation.
- There is no provision of punishment/culpability to sponsors, investigators, ethics committee members and government. There is no punishment for inaction

especially after having received information about serious violations, except that the sponsor can be debarred from conducting further clinical trials.

- Further, there is no mention in these guidelines about compensation in case of negligence and dereliction of duty on the part of all those involved in clinical trials or deviation from protocol, etc. Indeed, in these cases, the compensation should be higher than that calculated from this formula.
- The cases that are not considered SAEs but are nevertheless still disabling have not been addressed in the present framework.
- There is also no reference to the cases of death that occur long after the clinical trial is over. There is no mention about teratogenic cases, inter-generational, latent problems which might occur in the third generation.

7.2.4. Issues with the formula devised for calculating compensation

The use of the Workmen's Compensation Act (1923) that calculates the quantum of compensation based on the age of the injured in case of permanent disablement and death is inappropriate in a clinical trial setting. The whole purpose of the Workmen's Compensation Act is to compensate a worker who is injured while on duty. The compensation is also dependant on the percentage of injury or disablement. It is for workers who get a regular salary/income and many other benefits and emoluments, bonus, etc. To link the formula in the Workmen's Compensation Act to injury or death during a clinical trial is fallacious and incorrect. In a clinical trial setting, the participants are not workmen or labour, the industry does not hire them on a regular basis and there is no employer-employee relationship between the participant and the sponsor/industry/academia/institute conducting the clinical trial. Linking participants in research to "workmen" would be unethical. It may act as coercion to the participants to feel obliged to remain

Amount of Compensation = B X F X R / 99.37

Where

B = Base amount (i.e. Rs 8 lacs)

F = Factor depending on the age of the subject (based on Workmen's Compensation Act, 1923)

R = Risk Factor depending on the seriousness and severity of the disease, presence of co-morbidity and duration of disease of the subject at the time of enrolment in the clinical trial between a scale of 0.5 to 4 as under:

- 0.50 terminally ill patient (expected survival not more than 6 months)
- 1.0 Patient with high risk (expected survival between 6 to 24 months)
- 2.0 Patient with moderate risk
- 3.0 Patient with mild risk
- 4.0 Healthy Volunteers or subject of no risk

in a clinical trial despite any discomfort and distress. Multi billion dollar companies – in research – should minimise the possibilities of exploitation, unfair level of benefits and unfair level of burden of risks.

Thus, the mechanism for compensation is still far from being a robust model, which can ensure that the clinical trial participants who suffer from the adverse events get compensated in a just manner. Further, as seen from the responses of both key informants and especially the clinical trial participants, there is a need to generate awareness about compensation in case of adverse events.

Post-Trial Access

Post-trial access (PTA) refers to the access to, and the availability of, the trial drug/medicine/treatment even after the trial is over. On the one hand, the clinical trial participants risk their life and experience other research-related burdens, and hence they are likely to feel entitled to some benefits, which can be in the form of PTA to the drug. As Doris Schroeder (2008) describes it succinctly that the duty of research sponsor to provide a successfully tested drug after the trial has been completed to research participants who took part in the clinical trial.⁷⁹

The health status of patients is affected by their participation in clinical trials and they experience a sense of loss when at the end of the trial, access to the trial drug is denied to them. In the context of clinical research, a question that concerns many of the stakeholders in the study is: “What will happen once the research study is over? Researchers and sponsors increasingly confront the issue of whether participants in a clinical trial should have PTA to the trial drug”. The issue of PTA is also relevant because externally sponsored research in developing countries raises ethical issues not only during the research study but also once it is over.^{80 81}

Legislation and guidelines are inconsistent, ambiguous or silent about many aspects of PTA. This section explores the perceptions and opinions of clinical trial participants about whether or not, and why, they should receive post-trial access to the trial drug, care and information along with the opinions of the key informants.

8.1. Access to the Trial Drug: Concerns of the Clinical Trial Participants

Many CTPs thought that they should receive access to the trial drug or to a therapeutic “equivalent” if such access would be beneficial. Some of the participants who perceived having benefitted from the trial expressed anxiety about the prospective discontinuation of the drug after the completion of the trial period. Sharing his anxiety, a CTP from Gujarat said:

Currently, I am taking three injections in a week. I can see an improvement in my health condition. But I am a little worried now. In case I require the same medicines later on, how will I avail them? [GJCTP12]

The issue of PTA becomes all the more relevant for participants suffering from a disease for which there is currently no cure available. With the knowledge of the prospective discontinuation of the trial drug and of being put on standard treatment, a participant suffering from an auto-immune disorder said that the trial drug should be made available:

Yes, I feel that this treatment is helping me and that I am able to control [the] itching and I think the patches are subsiding. I am happy about it. But I was told that the trial is till next year and then we will be back to our normal treatment. I hope in this period I will have some relief. I also hope that the drug is continued on us. It should be [made] available to us in the OPD freely so that poor people like us get benefits. For me it was a good medicine. [APCTP2]

The other CTP from Delhi who was part of the clinical trial raised an interesting issue of PTA to the community and not just to the research/clinical trial participants:

If we are a part of any trials related to HIV, the drug if it worked well during the trial or showed any improvement should be made available to a wider group not only to those who took part in the trial. It should be beneficial to the community as well not just to an HIV affected person. [DLCTP1]

In a situation of the prospective non-availability of the trial drug after the completion of the trial period, some of the participants expressed their willingness, albeit reluctantly, to purchase the trial drug. They also expressed their expectation about the affordability of the trial drug after the completion of the trial process. Expressing their anxiety about the affordability of the trial drug, some of the participants said:

I wish and hope this medicine will be available to people like me suffering from this disease also. This injection should be made available at lower costs at [the] chemist soon. [APCTP1]

The trial is for one year. I feel that the medicines should be made available free of cost even after the trial is over. [APCTP3]

I require the experimented drug later on. How will I avail it? . . . If my haemoglobin continues to [fall], then I will require more injections, but it will become very expensive for me. [GJCTP12]

Participants were also concerned about any AE occurring after the trial. According to a participants from Gujarat:

But I am a little worried now. In case I develop any side effect in the long run, who will provide the treatment after the trial period? [GJCTP12]

The perspectives and views offered by the KIs reveal that most of them agreed in principle with the idea of providing PTA of the trial drug to the participants if proven beneficial. Speaking in the context of providing PTA to the participants, a Clinical Research Coordinator from Gujarat said:

It is a good idea and it would be good if something like this would happen. [GJCRC1]

Expressing his favourable attitude towards providing PTA to clinical trial participants, another CRC from Gujarat stated:

It would be better if they have access to the medicines post-trial also. [GJCRC3]

However, two questions arise: How can accessibility be ensured and how broadly can the product be made available? Should access be limited to those at risk for acquiring the infection or be extended to the general population?

8.2. PTA- A “complex” issue

PTA is a complex and multifaceted issue that deserves careful consideration. On the one hand, the KIs expressed their favourable attitude towards providing PTA to the participants, but, on the other hand, they also expressed their limitations in actually facilitating the process. The decision about providing PTA, as expressed by most of the PIs, was dependent on the sponsor.

According to two PIs from Delhi:

Usually, the sponsor approves it, but we have to ask for permission. Everything depends upon the costs and [the] economics of it all. [DLPI1]

Whether the drug should be [made] available later on to the participant or not should be left to the discretion of the sponsors. [DLPI2]

On the one hand, the PIs acknowledged that the decision to provide PTA lies with the sponsor, and, on the other hand, they also admitted that various other factors play a role in allowing PTA to participants. The demand for making the trial drug available after the completion of the study period was considered “wishful thinking” by one of the PIs, because getting the trial drug to the market is a time-consuming process. Speaking about the duration taken to introduce a trial drug in the market, a PI raised a pertinent question related to the issue of PTA:

If the drug is useful, then it should be [made] available to the patient even after the trial period [but this] is wishful thinking. However, I don't think we can say this for certain, as the marketing and licensing of a new drug takes many years. But for how long should the drug be provided is also a question [that needs to be addressed]. Since cancer drugs are very expensive, those that are proven [to be] beneficial to the patient should be [made] available at subsidised prices so that even the middle class and [the] poor can access them. Hence, PTA is an important issue and requires further discussion, including policy-level changes. [APPI2]

Speaking about providing PTA to chronically ill participants, the PIs further questioned the duration for which the trial drug should be provided to the participants.

According to a PI from Delhi:

In most cases, if the patient finds the treatment beneficial, he/she will come up with the question. Then we explain to them that the medicine will only be available for one year of the enrolment. There is also control group where the drug is not given, so accordingly they have to be reminded time and again that the drug is available only for a limited time period. [DLPI2]

Further, getting the trial drug to the market requires a long procedure and is a time-consuming process. Pointing to the complexity of the issue of PTA, a CRC said:

It is very tricky. The trial drug can take [a long] time to come to the market, so, that particular drug is not available to the patient. [APCRC1]

A Sponsor expressed similar concern. He mentioned:

It is very important to understand the process of getting approvals for licensing and marketing from the regulatory authorities. It may take many years to get approval for the drug for marketing. It might be [too] late for the trial subject to access this particular drug for which he or she was a subject. This needs to be considered in any discussion related to PTA. [SP]

Additionally, providing PTA means a clearly reduced profit margin for the sponsor/ pharmaceutical industry, which is highly profit oriented. As one of the CRCs stated:

As of now, I have not seen any sponsor who has allowed post-trial access to patients of drug trials. I feel that it would not be feasible for many sponsors as it also eats into their profits if they have to provide post-trial drugs to every participant who was part of a global trial. [GJCRC1]

Another factor that prevents or deters sponsors from providing PTA to the participants is the need for testing the efficacy of the trial drug. Talking about this, a PI from Maharashtra said:

Post-trial access is also a huge problem, and I feel that the least the sponsors can do is to provide the participants with the drug at a subsidised rate, if not free, once the trial is completed and the drug is found to be safe and efficacious. [MHPI1]

Speaking in the context of benefiting participants, two PIs from Maharashtra and Andhra Pradesh said that the participants were put on standard treatment after the completion of the clinical trial process. Speaking in the context of clinical trials in rheumatology, the PI from Maharashtra stated that he recruits participants who are

unable to pay for the expensive drugs after which he puts the participants on standard treatment:

Since this hospital caters largely to poor patients, a large majority of my patients who come to the rheumatology OPD cannot afford the new-age 'biologics' treatment for arthritis. These new treatments go beyond the use of disease-modifying agents and are generally more expensive medications given in injectable form when patients stop responding to oral medications. This treatment is extremely expensive and is unaffordable to almost all my patients. Thus, when we get a proposal to conduct a trial using this form of treatment, we consider it for the benefit of our patients. In most cases, we have already given them a combination of two–three oral drugs to which the patient is not responding and hence [the patient] needs to be put on IV drugs, which is out of their purview because it is expensive. These patients can be brought under the trials. However, it is true that post-trial access . . . But with rheumatology, it is such that two–three doses of the biologics treatment is sufficient to make the patient disease free, after which the patient can be put back on oral medication, which acts in a better way as inflammation has been reduced. The other motivations for us to take on these trials is definitely our own research motivations as well as [the fact that as] PIs we get to know of the more recent treatments and [the] new drugs. [MHPI4]

Speaking along similar lines, another PI stated that after the closure of the clinical trial, the participants are put on standard treatment:

After the close of the trial, the patient continues with regular treatment. The end point of any study is patient improvement and to ensure a range of improvement. So if the trial results in improvement, then most patients go into a suppressed-disease state and may not require any further treatment. If the drug is not helping, then there is no point in continuing [with it]. Thus, the trials are designed accordingly for a time period of about a year [in order] to record [the] maximum change. [APPI3]

Contrary to the general ideas widely in favour of PTA, a PI from Gujarat said that he is not in favour of PTA. He further stated that the duration of a clinical trial period is usually four or five years during which the trial drug is provided free of cost to the participants:

I think it [PTA] is not necessary. The subjects receive the trial drug for free for almost four–five years. The PI and the team are remunerated for the trial, so I do not know how much post-trial access could be made feasible. As such, patients are randomised into placebo-controlled and those on study drugs. [GJPI1]

However, a point that is not taken into consideration by the PIs is that the participants take a risk by the very act of enrolling in a clinical trial, especially when it is not known whether the drug would work or not. Moreover, there is the possibility of AEs and sometimes even death. However, when the drug is found to be effective, access to the drug is denied to the participants. It is also important to distinguish between the risk taken by the sponsor and the risk taken by the participants. The sponsor risks financial resources whereas the participants risk their bodies that are already in a diseased condition to test the drug. Hence, issues relating to PTA need further deliberation and should not be summarily dismissed as a simple matter.

Interestingly, a sponsor interviewed described an instance in which the trial drug was provided to the participants on a lifelong basis. He recalled:

We have only one instance where we decided to do a study with an inhaled drug (antibiotics) for patients with cystic fibrosis where there was no commercial interest in launching the formulation. Hence, before we consented to participate in the trial, we agreed to provide patients enrolled in the study lifelong free inhaled drug, which was the study drug. Standard of care is usually not provided. [SP]

Speaking about the process of making a trial drug accessible, he added:

Based on recommendations from the treating physician, an experimental drug can be made available using a T-license before being granted market authorisation. [SP]

The following discussion from an interview with a PI from Andhra Pradesh, which clearly indicates that there can be an undue inducement in the context of post trial access to treatment:

Researcher (R): Do you think post trial treatment is important to the patient participating in the trial?

PI: Yes. It is very very important and it should be designed as a part of the trial protocol and should be a part of informed consent process only when it is appropriate.

R: How do you decide appropriate?

PI: It is necessary to consider the factors such as the disease and the type of molecules used in the trial.

R: Do you think whether post trial access might constitute undue inducement for patients to participate in the study?

PI: Some PIs will recruit patients by giving them false promises that the trial drug will be available to them even after the completion of the clinical trial. Many patients who are desperate for treatment for certain diseases will immediately say "yes" hoping that they will get access to the drug even after the trial period gets completed. This is clearly exploitation; you are taking an advantage of the vulnerability of the patient because you need more number of subjects required for your sample. [APPI5]

8.3. Post-trial obligations under current law and guidelines

There is no mention of PTA in the Informed Consent Form listed in Schedule Y of the Drugs and Cosmetics (Third Amendment) Rules, 2013. The Indian Council of Medical Research (2006) also maintains an ambiguous stand on PTA and states:⁸²

Whenever possible I/EC should consider such an arrangement in the a priori agreement. Sometimes more than the benefit to the participant, the community may be given benefit in [an] indirect way through

improving their living conditions, establishing counseling centers, clinics or schools, and giving education on maintaining good health practices. For smaller scale or student projects post trial benefit to the participants may not be feasible but keeping in mind the post trial responsibility conscious efforts should be made by the guides and the institution to initiate steps to continue to support and give better care to the participants.

However, in the section on Special Concerns, ICMR guidelines state:⁸³

iv. Post trial access to the vaccine should be available to the control group. But if the vaccine is for paediatric age group and by the time the study gets over the children in the control arm may cross the age when the vaccine is supposed to be protective. In such instances the control arm could be some other alternative vaccine for that paediatric age group although this does not restore clinical equipoise. EC may examine the feasibility and ethical aspects on a case-to-case basis.

v. Post trial access to the vaccine should be given first to the community from which the participants were drawn.

However, ICMR Guidelines do not mention that informing about post trial treatment to the participant is a mandatory requirement. The Guidelines are also completely silent about the need for informing participants about PTA during the consent-taking process.

There are two other significant international guidelines, which are relevant in the context of post trial obligation; The Declaration of Helsinki of the World Medical Assembly (WMA) and the CIOMS guidelines. The revised Helsinki Declaration (2013) states:⁸⁴

In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process. (Principle 34)

Generally and in practice, there seems to be a recognition of moral responsibilities for PTA. However, post trial access should not be limited only to the interventions identified as beneficial but also to treatment for any post trial adverse events.

CIOMS 2002⁸⁵ demands that *'Any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.'*

The obligation of providing the PTA lies with the sponsor. Assuring PTA for the investigational product, which is yet unlicensed would obviously require a nod from the regulatory authority. However, PTA with standard treatment should not be a problem but the issue must be decided before the clinical trial begins with full and proactive cognisance of other actors- the IEC, the PI, the regulatory authority and the health system.

Discussion

From the participants' perspective, the interviews clearly indicate that post trial access to drugs was not discussed or mentioned during the consent taking process.

Thus, the issue of PTA raises questions at different levels. At the policy level, it is argued that the cost of PTA will increase the transaction costs of clinical trials, potentially deterring beneficial research from being undertaken and limiting the number and kind of studies pursued. Further, where there is a minimal health care support system, the cost of PTA access cannot be selective, and there is a possibility that the sponsor may be wary of undertaking research in these areas.

At the legal level, sponsors and investigators are concerned that expanded PTA will expose them to greater risk of liability, as there are concerns about the monitoring procedures to be followed after the clinical study is over and about post-trial claims. It also needs to be discussed whether the relationship can be adjudged as a patient-doctor relationship or as an investigator-subject relationship. Finally, at the ethical level, it is the investigator's duty to not abandon the participant once his "useful life" to the investigator or to the sponsor is over.

However, post trial access also raises practical implementation challenges such as; what does PTA imply in the cases of unsuccessful clinical trials? What happens when a trial is terminated? Or if the new product is withdrawn from the market?

It is also important to discuss PTA in the different phases of clinical trials. The benefits are also dependent on the phase of the clinical trial. In Phase I, participants are mainly healthy volunteers and often face high risks with low chances of returns, which further emphasises the need for alternative benefits. What PTA arrangement would benefit these participants? The type of disease, the type of drug and the type of trial are equally important. For example, in what type of clinical trial is PTA absolutely necessary?

Safety of the drug is another issue which needs to be addressed in the context of PTA. What if the medicine doesn't prove to be safe after marketing?

It is necessary to examine post trial access in the larger context of public health in India. Out of pocket expenditure on health care which forms a large proportion of health care expenditure and poverty are strong push factors that can result in people choosing to participate in clinical trials due to poor access to medicines, and lack of health care. Post trial access is one area which needs more attention in India through clarity in regulators and ethics committees ensuring that PTA is discussed early in the clinical trial prior to a clinical trial being provided permission. Also this should be reflected in the consent documents, ensuring that this is indeed done should be followed up.

Conclusion

This chapter highlights the significant findings of the study and discusses key areas emerging from it.

Section 9.1

9.1.1. Health-seeking behaviour

The findings point to the health-seeking trajectories of the participants — the recourse to multiple referral chains of local healers, alternative-therapy practitioners, general practitioners, and specialists, but not necessarily in this order — informed and shaped by health care professionals as well as by their own personal contacts. Aggrieved by their health condition and non-availability of requisite and affordable care, such referrals resulted in the participants expending more time, money and energy in the search for treatment. This further contributed to increased desperation and vulnerability. For example, the lives of participants suffering from psoriasis were deeply affected by their health condition and the associated social stigma. The distress and helplessness stemming from these conditions were the reasons given for their participation in clinical trials, i.e., the hope of receiving improved and effective treatment and cure.

9.1.2. Reasons for participation - pull and push factors

While the study sample points to a diverse socio-economic profile, the study findings reveal participation on a considerably large scale by those from lower socio-economic groups. Economic reasons are one of the strongest and most compelling push factors that influence the decision to enroll in clinical trials. This is compounded by the lack of access to affordable and quality health care through the health care system. Participants also articulated “altruism” as a push factor, i.e. their perception of the clinical trial drug being of benefit to others.

“Free treatment” and access to “new treatment” are strong motivating factors for participation in clinical trials. Some of the participants enrolled in the clinical trials because their treatment at the time was perceived as not being effective and were hopeful that the drug being tried would be beneficial. Another strong pull factor is the doctor’s influence on the patient’s decision to participate in the clinical trial. This influence emanates largely from the typically hierarchical relationship between doctors and patients as well as the trust that is largely reposed in the doctor’s judgement with regard to the latter’s health.

9.1.3. Recruitment of clinical trial participants

Participants were mostly recruited through the outdoor-patient departments (OPDs) of health facilities, and the treating doctors there were also frequently the principal investigators (PIs) of the clinical trials. This raises a very serious issue, that of the conflict of interest of the doctor who also assumes the role of the PI in a clinical trial. The doctors often persuade their patients to be recruited as clinical trial participants and provide assurances about the trial drug’s beneficial effects on their health condition. There is an urgent need to put in place mechanisms that will address this conflict of interest and inherent bias to ensure that recruitment is fair. The onus rests with the doctors, and also with all the actors involved in the conduct of clinical trials, to ensure that the distinction between clinical trials and standard treatment is made clearly and unambiguously, and that this distinction is explained to the patients in simple language that they can understand. Therapeutic misconception is a key issue of concern as it foregrounds the participants’ comprehension of the clinical trial itself, a matter that has been raised and emphasised throughout this report. Therefore, the responsibility of ensuring that there is no misguided perception amongst potential participants about the clinical trial as “treatment” lies entirely within the ambit of the protocols of clinical trials and is also a responsibility that lies with those involved in the conduct of these trials.

This situation also does not imply that there would be no therapeutic misconception if the doctors were not also the PI of the study. However, the instances of therapeutic misconceptions occurred more frequently when an individual played the dual roles of a physician and an investigator.

9.1.4. Informed consent

The findings also point to the true nature of voluntary consent having been compromised despite informed decisions being made by some of the participants. The voluntariness in most instances was affected either by the influence of the doctor or the PI or by other influential individuals in their lives (husband, sister, friend, etc.) who convinced them to participate in the clinical trial. Additionally, as mentioned earlier, their deteriorating health condition and the non-availability or non-affordability of treatment also compelled them to participate, a situation that raises fundamental questions about the very basis of “free” and “voluntary” consent.

This was evident also in the processes of consent seeking and giving. The unquestioning trust reposed by the patient in the doctor, and the influence of other socio-cultural norms, including gender norms, tend to compromise active participation and voluntary decision making. The consent processes must take into account the implications of these norms for promoting voluntary and informed consent. There must be no ambiguity in the communication or the exchange of information, so that the potential participant can fully grasp that he/she will be given a trial drug on the basis of the clinical trial design and that this trial drug may or may not benefit him/her. The requisites of true consent are discussed below:

Assessing the capacity of the participant: The decision-making capacity of participants varies across populations, influenced by factors such as the age, sex, and gender, whose health condition undermines or limits their capacity to consent or take a decision, and therefore an individual assessment of a participant’s capacity to consent is both essential and meaningful.

Providing relevant information about the clinical trial: The information disclosed to the participant should be honest and complete, and should include information about the risks and benefits of the clinical trial. It was found that some people had participated in clinical trials involuntarily, as the doctor had not given them full and complete information, or had given them no information at all. Sometimes, the information given by the doctor was biased, being too definitive about the possible benefits of the drug/vaccine being tested, thereby hugely compromising the consent process.

Ensuring that the participant understands the information: The cognitive processing of information, both received and provided, should be done in a manner and in a language that the participant understands. This is particularly important in terms of the ability of the PI (and of the other actors involved in the conduct of the clinical trial) to describe in simple terms, to the participant, the risks and benefits of the clinical trial, and to explain the concept of the controlled experiment. It was found that participants, despite having read the consent form, could not recall its contents, or were confused between the consent form and the patient information sheet, or had failed to understand the consent form. They were unable to recall the risks that they had agreed to undertake in participating in the trial. It was found that some of the participants had signed forms that they were unable to read or understand.

Ensuring that the participant voluntarily chooses to enter the clinical trial: To evaluate voluntariness, it was important to assess the awareness of the participant at the time of consent giving and taking that participation in the clinical trial was purely optional. It appeared that patients were asked to “opt out”, as they were aware that they could withdraw from the trial. But whether they voluntarily “opted in” the clinical trial is a claim that needed to be tested. For those who had a medical condition with no treatment, the options were limited, and this reality or fact influenced their final decision making. Some doctors and coordinators discussed the matter with the family of the participant and helped them make a decision and also explained all the options available to the potential participant.

Gender norms also came into play, thereby affecting voluntariness and influencing decision making in the context of women participants. An understanding of these norms and the resulting gender dynamics is important for facilitating a process of consent that is truly informed and voluntary. Hence, the PI, or the person who recruits the patients, should be oriented or trained to understand the socio-cultural context of the potential participants, which has a bearing on the recruitment process. PIs or recruiters often have to approach “gatekeepers” of the family and to be cognisant of the gender or family dynamics resulting from power asymmetry within families. This is necessary to ensure that adequate efforts are made to enable the active participation of the participants in the consent process, without foregoing their right to information and consent.

Ensuring that the participant provides written consent: Authorisation regarding enrolment was given through written consent, that is, the signature or thumb impression on an informed consent form. Most of the participants had signed the informed consent forms when they were enrolled in the study. However, the signing of the form was not tantamount to giving legally recognised informed consent. It was also found that lengthy consent forms were primarily perceived as safeguarding the interests of the sponsors and the PIs, rather than protecting and promoting the rights of the participants. The interviews of participants revealed that they were merely passive participants in the informed consent process. Most of the participants could not exercise their agency to ask any questions when they had not understood many technical terms in the informed consent form. Sponsors expressed their inability to ensure that informed consent is taken in a proper manner. However, it was found that there is no system to assess whether the participant has comprehended the information in the consent form. Some key informants have suggested the following: shortening the informed consent form; using simple language that is understood by the participant; recording the procedure through writing and video recording. Given the concerns around privacy and confidentiality, manipulation and storage with regard to video recording, it is necessary to examine and debate this option further.

The perspectives of participants and those of the KIs reflected clear differences in the levels of information about the clinical trial process that were made available to them, a situation that has serious implications for consent. The KIs' perspectives underline the multiple issues and areas vis-à-vis clinical trials that need to be addressed urgently to ensure that they are conducted in an ethical manner as well as to ensure that the rights of participants are not violated. This includes ensuring that participants have access to comprehensive information about the clinical trial, including about AEs, towards facilitating their informed consent for participation. Alternative methods of obtaining informed consent, such as witnessed consent using a third party, could be used in some cases. It is critical to reduce the in-built asymmetry of power in order to promote the agency of the participant. Further, in the context of clinical trials, access to long-term health care, insurance, compensation, post-trial access to medicines, and other entitlements to participants must be recognised as rights, and not as tiresome obligations, and nor should they be used as incentives for participation.

9.1.5. Adverse Events (AEs) and Compensation

The study findings showed that some participants had experienced dizziness, fever, headaches, pain in chest, etc. Participants were given limited information about the AEs that they may experience in the course of the clinical trial, as well as the possible long-term adverse reactions. Clinical trial participants were expected to identify the adverse events and serious adverse events (SAEs) themselves and to report these events to the doctor. Therefore, it appears that the PIs do not conduct a regular check-up and nor do they follow up to report or document the AE and the SAE systematically.

There was discrepancy in the responses of the KIs regarding the time duration within which the AE should be reported to the Drug Controller General of India (DCGI). So while some of the KIs said that the AE should be reported to the EC members and the DCGI within 24 hours of its occurrence, other KIs reported that the duration should be between seven and 14 days. When AEs are not reported to the clinical trial sponsor and/or the authorities, it means that the safety data of the experimental drug is actually compromised, which raises grave concerns about the safety of the drug once it enters the market.

It also appeared that the AEs were recorded primarily to give a report to the sponsor, the EC, the DCGI, etc. If linkages were made properly, compensation also could be claimed and given in an appropriate and timely manner to participants. It was seen that the vast majority of the AEs were recorded as being not linked to the trial and therefore no compensation was provided.

It is the responsibility of the PI to report AEs as he/she has the role of the primary care giver to the patient. The reporting of the AE to the authorities, such as the DCGI, by the PI and the CRC was supposed to be done within a stipulated time period following the occurrence of the AE. However, in the case of any issues or in instances of non-reporting, there were no mechanisms in place for the participants to be able to report AEs. The absence of systematic reporting also has critical implications for the award of compensation.

The interviews revealed that the participants were often unaware of compensation. Most participants had no knowledge of the element of compensation or insurance.

Even those who had stated that they had read the consent form and were satisfied with the information provided therein were unable to articulate their thoughts on compensation.

There was considerable confusion and disagreement amongst the KIs about the way in which compensation should be handled. The compensation in trials for AE, SAE, and death of the clinical trial participant should be determined prior to the commencement of the trial. The Sponsor should be primarily accountable and responsible for compensation and should along with all the actors involved in clinical trials — such as the investigator, ethics committees, regulatory authorities and the health care system — ensure that the participants are compensated adequately, on time, without unnecessary delays.

9.1.6. Post-Trial Access

A question that many participants involved in a clinical trial ask is: “What will happen once the research study is over?” The issue is relevant because externally sponsored research in developing countries raises ethics issues not only during the research study but also once it is over. Some participants who perceived that they had benefitted from the clinical trial expressed anxiety about the prospective discontinuation of the drug after the completion of the clinical trial period. This issue of post-trial access becomes all the more relevant for participants suffering from a health condition for which there is currently no cure available. On the one hand, participants risk their life and experience other research-related burdens, and hence they are likely to feel entitled to the benefits—whether in the form of reimbursement or post-trial access to the drug. On the other hand, the sponsor places more value on profits, and hence is not likely to want to continue providing the medicine free of cost beyond the clinical trial period.

Although some of the study participants expressed their satisfaction with their respective decisions to be part of clinical trials, many ethical concerns remained unresolved or unaddressed. The extensive interactions between the patients and the clinical trial team, including doctors, seem to have created an environment of obligation on the part of the patient towards the doctor, even when there may have been no overtly expressed intention on the part of the latter, or a sense of privilege on

the part of the patient resulting from preferential treatment. These conditions do not foster independent and unbiased decision making about participation in a clinical trial. We need to be cognisant of the typical clinical care setting in India, characterised by unquestionable trust reposed by the patient in the health care provider, and an inherent asymmetry in power that stems often from the patient's sense of obligation and gratitude, lack of medical knowledge, and lack of confidence when it comes to questioning or doubting any advice received from the health care provider.

Thus, the lack of access to affordable health care in the country, combined with the government policy of encouraging clinical trials and the absence of a comprehensive and strong regulatory framework for the protection of the rights of clinical trial participants, is bound to result in further violations of the rights of individuals who are treated as "experimental subjects". These concerns emerge frequently in the responses of participants who were part of the current study. Additionally, there is an urgent need for mechanisms to be put in place for the independent monitoring and reporting of clinical trial processes to ensure that the perspectives and concerns of clinical trial participants are included.

Recommendations

Clinical trials are the foundation of the process of drug development, and as such they raise serious concerns about ethical and safety issues, especially when the clinical trial participants (CTPs) are poor, inadequately informed, insufficiently protected, and vulnerable, and are therefore often not in a position to assert their rights and to claim their entitlements. In the absence of effective regulation, the necessary processes of clinical trials and drug development risk coming into disrepute. This is evident from the increasing violations of the rights of participants that have been highlighted by health networks, women's groups and non government organisations. This chapter presents certain recommendations based on the study findings and outlines future areas of inquiry.

10.1. Protecting participants' rights

10.1.1. Any mechanism to regulate clinical trials must ensure that the rights of clinical trial participants, particularly those from marginalised populations and from other vulnerable sections, are protected at all times and that robust provisions are created to safeguard this goal. Issues and concerns around informed consent, ethical review, monitoring of AEs, SAEs, etc., need to be identified specifically and detailed in any such law.

10.1.2. All clinical trial sites should possess and provide the necessary medical infrastructure and human resources required to respond quickly and effectively to any AEs that may arise in the course of the clinical trial. Currently, there are no specific, listed legal prerequisites for clinical trial sites, such as the availability of expertise and infrastructure to deal with unexpected AEs, emergencies, etc. The approving authorities—such as the Drug Controller General of India (DCGI) as well as the ethics committees—and the other responsible parties must ensure that these conditions are met prior to the grant of approvals.

10.1.3. The recruitment of a potential participant from the OPD of the treating physician poses an immense risk, that of therapeutic misconception. Hence, a

physician who is also the PI should not be allowed to recruit participants from his/her own OPD.

10.1.4. A charter of clinical trial participants' rights must be developed, must be made justiciable, and the information must be provided pro-actively by all the parties responsible for the conduct of clinical trials.

10.2. Ensure reporting, treatment, and compensation in the case of injury or death during trials

10.2.1 Sponsors should be required to provide comprehensive health insurance for all participants in order to cover all their health care needs, including ancillary care.

10.2.2. The DCGI must ensure that the sponsors and the principal investigators send prompt notification of all adverse events, injuries or deaths in a clinical trial, followed by a thorough investigation and necessary follow-up action.

10.2.3. Close scrutiny of all reports must be conducted to ascertain and ensure that participants are provided immediate and long-term medical treatment and that compensation is given for injury or death. Details regarding compensation must be finalised before the start of any clinical trial.

10.2.4. In the case of any clinical trial-related injury, disability, or death among participants, the law should mainly hold the Sponsor along with other actors involved in the conduct of clinical trials, accountable and liable.

10.3. Ensure post-trial access

The drugs developed through clinical trials in India that are proven safe and are approved for treatment must be made available free of cost to the participants until such time that they become available in the country through the health care system or at an affordable price. Sponsors must be required to sign an agreement to this effect.

10.4. Ensure transparency and accountability

10.4.1. All clinical trial-related information and documents—including applications, protocols, informed consent forms, information about the sites of clinical trials, ethics

review decisions, Adverse Events and follow-up actions, and both positive and negative outcomes—should be available in the public domain. The guidelines/protocols/requirements/regulations of the Clinical Trials Registry-India (CTRI) should be modified to enable better tracking of changes in the reporting of clinical trial-related data.

10.4.2. The culpability of sponsors, PIs, members of the EC, and government personnel should be upheld when they do not exercise the requisite regulatory oversight, especially after they have received information about serious violations, or if violations of ethical guidelines are not addressed.

10.5. Research agenda

10.5.1. Further research to document the experiences of clinical trial participants is necessary, as there have been very few studies in this regard in the country.

10.5.2. More research to document cases of clinical trial violations is required in order to develop best practices for conducting clinical trials.

10.5.3. Studies with a gender focus are necessary in the context of clinical trials (other than those such as research on contraceptives exclusively targeting women) in India. There is no documentation on the gendered experiences of participants as also, for example, on the proportion of CTPs who are women.

10.5.4. The experiences of CTPs with regard to the process of compensation should be studied in the context of the new amendments and formula that have been adopted.

10.5.5. More studies on the role and functioning of ethics committees are needed because these differ widely from institution to institution.

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⁴³ Sama has an organisational Ethics Committee (EC) to ensure a comprehensive review of all ethical aspects of the research project. Seven EC members from multidisciplinary backgrounds, a mix of medical/ non-medical, scientific and non-scientific persons including lay persons were nominated in compliance with the ICMR guidelines for constituting this Ethics Committee.

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⁶⁵ Directorate General of Health Services, Ministry of Health and Family Welfare. (19 November 2013). Order. F.No. GCT/20/SC/Clin./2013 DCGI. Available at [<http://cdsco.nic.in/Office%20Order%20dated%2019.11.2013.pdf>] accessed on

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⁶⁷ Munshi, R., & Thatte, U. (2013). Compensation for Research Related Injury. *Perspectives in Clinical Research*, 4(1), 61-69.

⁶⁸ The 'Good Clinical Practices [GCP] for Clinical Research in India' guidelines has defined adverse event as: any untoward medical occurrence (including a symptom/disease or an abnormal laboratory finding) during treatment with a pharmaceutical product in a patient or a human volunteer that does not necessarily have a relationship with the treatment being given.

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⁷⁰ According to Notification GSR 53(E), a serious adverse event is an untoward medical occurrence during clinical trial that is associated with death, in patient hospitalization (in case the study was being conducted on out-patient), prolongation of hospitalisation (in case the study was being conducted on in-patient), persistent or significant disability or incapacity, a congenital anomaly or birth defect or is otherwise life threatening.

⁷¹ Clinical Trials in India (30 August 2013): Ministry of Health and Family Welfare (Government of India). Available at: [<http://mohfw.nic.in/index1.php?linkid=338&level=1&lid=1640&lang=1>] accessed on 28 November 2013.

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⁷⁶ Please note that data on the perspectives of the key informants regarding compensation has been collected before recent changes in the context of compensation.

⁷⁷ Formula to determine the quantum of compensation in the cases of clinical trial related serious adverse events (SAEs) of deaths occurring during clinical trials, vide GSR 53(E) dated 30-01-2013 inserting a Rule 122 DAB and a new Appendix-XII in Schedule Y, available at <http://cdsco.nic.in/> accessed on 23rd, December, 2013.

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