

“The invisible”: Participant’s experiences in clinical trials

Sarojini Nadimpally, Divya Bhagianadh

Sama Resource Group for Women and Health, New Delhi, India

Abstract

Background: The paper discussing the perspectives of clinical trial participants about the various aspects of CTs is based on the primary research conducted by Sama in 2012-13.

Methodology: In-depth interviews were conducted with 36 CT participants from the states of New Delhi, Gujarat, Maharashtra and Andhra Pradesh. In addition to CT participants, other key informants including investigators, representatives of Contract Research Organizations (CROs), sponsor, Ethics Committee (EC) members etc. were also interviewed to develop a comprehensive understanding of the functioning of the CT sector.

Findings and Discussion: The paper describes the perspectives of participants on the relevant aspects of recruitment into CTs, reasons for participation in CTs, informed consent, adverse events and compensation. The role played by the push and pull factors in recruitment, the information asymmetry, the power imbalance between the health-care provider and seeker, the role of sociocultural factors, etc., are explored in the paper. Combined with the insights from other stakeholders, the study gives an understanding about the chasm between regulations and realities in the Indian CT sector. Further, the paper briefly explores the recent changes and amendments in the laws governing the CT sector that is aimed at improving the conduct of CTs and uphold the rights of participants.

Conclusion: Participants are the most important stakeholders in a CT setting. It is imperative that their voices are heard and their rights upheld for the ethical conduct of CTs.

Keywords: Clinical trials, compensation, informed consent, participants, recruitment

Address for correspondence:

Ms. Sarojini Nadimpally, B-45, 2nd Floor, Main Road Shivalik, Malviya Nagar, New Delhi - 110 017, India. E-mail: sarojinipr@gmail.com

INTRODUCTION

The Government of India, after becoming fully compliant with the Trade-Related Aspects of Intellectual Property Rights Agreement in 2005, changed its rules in favor of the pharmaceutical companies to promote the conduct of new clinical trials (CTs) in the country. 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 CTs in India. It was felt this kind of “liberalization” would put India on the global

CTs map. Many major pharmaceutical companies and Contract Research Organizations (CROs) started conducting their CTs in India because of the relative cost advantage, ethnically diverse population, presence of premier medical institutions, and reliable human resources as well as an accommodating regulatory environment.

The growth of CT sector sparked many debates. While some focused on the immense financial and health-care opportunities that came with the trials, the direct and indirect benefits to Indian patients and the research sector in the country; some others pointed out the lacunae and areas of improvement.

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There has been a focus on the lack of enforcement of regulations, exploitation of inequities and structural factors, lack of protective mechanisms, and the nonalignment of clinical research sector with the public health priorities of the country.

In May 2012, the 59th report by a Parliamentary Standing Committee on the functioning of the Central Drug Standards Control Organization (CDSCO), India's main regulatory body for medicines and CTs, pointed to various irregularities in the functioning of the CDSCO. The report recommended major changes in the functioning of the office of the Drugs Controller General of India.^[1] The year 2012–2013 also witnessed the filing of Public Interest Litigations by civil society organizations with regard to the unethical practices in the conduct of CTs in the country and reiteration of the demand for compensation for CT subjects. Judiciary, media, and civil society organizations played an important role in prompting the CDSCO and other policy makers in making efforts toward strengthening the structures and processes toward ethical conduct of CTs. In the analysis of the compensation policies, the most important stakeholder - the trial participants, stood out by being the most invisible of all of them. This invisibility of participants is particularly so in the decision-making process.

It was in this context that Sama Resource Group for Women and Health conducted a multisite research study during 2012–2013 with the objectives of exploring the perceptions of CT participants and of understanding the various concepts and processes linked to CTs in India. The other objectives were to learn about the motivations for participating in CTs and also to develop a narrative about their experiences. The paper based on the study findings offer insights into how participants conceptualize their participation and the different processes associated with CTs. We tried to elaborate the experiences of participants through their trajectories/narratives while participating in CTs.

METHODOLOGY

The study sites included Gujarat, Maharashtra, New Delhi and Andhra Pradesh. These states were selected purposively to allow for the representation of the different geographical locations and since they had a high density of CTs and institutions where the trials were being held. In addition to participants, other key informants (KIs) including the principal investigators (PIs), representatives of CROs, sponsors of CTs, program managers and Ethics Committee (EC) members were included in the study to understand their insights on the conduct of CTs and perceptions about participants.

The interviews were coded and identifiers removed to maintain the anonymity and confidentiality of study participants.

In-depth interview guidelines and KI guidelines were used for interviewing the participants and KIs. Participants were accessed through the institutions and clinics both from public and private, where the CTs were taking place as well as through community-based focus group discussions in these states. The study was approved by the EC of Sama.

Profile of participants

Of the 36 in-depth interviews, 23 were held with men, and 13 were with women participants. Parents of two children, aged 1 year and above were also interviewed in the context of pediatric trials. The respondents were from diverse backgrounds in terms of caste, religion, education, and income. The majority of participants belonged to lower socioeconomic classes, had a higher susceptibility to illnesses but limited access to health care due to lack of affordability.

Recruitment

Recruitment is the first step of interaction with the CT participant. Recruitment methods for CTs vary from physician referrals to highly specific databases of patients to mass media advertising.^[2]

Patients passed through a complex network of multiple doctors, suggestions by friends and family before getting enrolled in the trial. It was aided by doctors did cross referrals depending on the nature of the trial and disease condition. Patients go through multiple forms of alternative treatments and spent significant money and other resources in search of a cure or relief from the ailment. Such participants, especially those with financial constraints had higher chances of agreeing for the “new treatment” which is “free of cost.”

The most common avenue of patient recruitment was found to be the outdoor patient departments (OPD) and indoor patient department. Majority participants shared that they were told about the trial when they visited the OPD or when they were admitted. The other methods were doctors' referrals, health camps, word of mouth, advertisements, nongovernmental organizations, agents, panchayat, and patients groups. Some trials also recruited patients from arogyasri insurance scheme.

“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).

At the time of recruitment, the physician recommendation was one of the primary factor influencing patients' decisions to enroll in a trial. This form of therapeutic misconception is

an important concern to be addressed as patients might end up confusing between a trial and treatment. The therapeutic misconception of research participant in CT is a situation where CT participants believe they are being provided the standard or best treatment. It could be because of many reasons, but the most important one is the reassurance from the treating physician who is also the researcher that the experimental drug is not risky and is a better form of treatment. This reiterates the ethical and moral duty of the doctor to inform the participant of the difference between treatment and experiment.

Reasons for participation

There are number of reasons that lead an individual to participate in CTs. A few of the CT participants stated that they participated in CTs as they perceived their participation as benefitting others. This was seen in patients suffering from cancer especially.

“I had some hope that this drug might help me and help others like me” (CT participant, Maharashtra).

A combination of push and pull factors motivates participation in CTs which are explained below.

Push factors

Economic reasons are one of the most compelling push factors to enroll in CTs even in the presence of alternative treatment.

“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” (CT participant, Gujarat).

KIs opined that educated urban patients with financial means are often reluctant to be part of CT with majority of participants belonging to rural areas with limited financial means.

Pull factors

Free medicines and free investigations

“Free treatment” is one of the strongest pull factors influencing trial participation. Even though a participant could afford the current treatment, availability of free treatment can still attract patients to get enrolled.

Access to “new treatment”

Access to “new treatment” is also another source of motivation for participation in CTs. Some of the CT subjects enrolled in CTs because their treatment at the time was perceived as not being effective or not working very well for them and they were hopeful about the drugs being tried. This perception was magnified by its reinforcement by doctors.

Trust in the doctor/influence of the doctor-patient relationship

Another strong pull factor is the doctor's influence on patient decision with regard to participation in the CT. This influence emanates largely from the hierarchical relationship between doctors and patients as well the trust that is largely reposed in the doctor's judgment with regard to latter's health. Trust is an essential, yet complex component of the CT dynamics. Participants narrated that doctor's “assurance” about the “new treatment” and it being the best option available to them played an important role in allaying their apprehensions about the experimental nature of the treatment being offered. Another matter of significance is the dual role of the caregiver as the investigator of a CT where patients feel obliged to take part in the trial perceiving a continuum of care by their doctor, which may not be available if they decline to be part of the trial. Hence, it is essential that an independent doctor not previously treating the patient attends to the CT participant and gives honest and complete information about the CT.

“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.” (CT participant, Maharashtra).

Informed consent

Informed consent represents the fundamental principles of research ethics and upholds the autonomy and capacity of the participant to make informed choices. Some of the major findings related to the informed consent process are discussed below.

Assessing the capacity of the participant

The decision-making capacity varies across age, sex, and gender of the participants. The medical condition also limits the capacity to consent or take a decision. It was observed that the practice of obtaining consent from the legal guardians in case of minors was strictly followed.

Disclosing relevant information about the trial

The interviews revealed that participants were not given detailed and complete information about the trial. Some interviewees mentioned a complete lack of information before enrolling in the trial. It was also found that information given by the doctor was often biased, being too definitive about the possible benefits of the drug being tested thereby compromising the consent process.

Ensuring that clinical trial participants understood the information

Information about the experimental nature of treatment being offered, the risks and benefits of trial participation, etc., should

be conveyed in a language that the participant could easily understand. However, there were lacunae in this understanding and some participants were confused between the consent form and questionnaire they had filled as part of the trial. Majority of the participants mentioned that they either signed the form without reading or comprehending the contents or viewed it as another formality. Consent in such situations cannot be considered voluntary, valid, or legal.

“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” (CT participant, Gujarat).

Investigators, on the other hand, talked about the difficulties in conveying information and ensuring whether the participant has understood the facts about the trial.

“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” (PI from New Delhi).

Ensuring the voluntariness of participant decision

While participants were aware of the option of opting out or withdrawing from the trial; whether the “opting in” process was voluntary or not needs to be examined more thoroughly. For participants with a medical condition, this decision is fraught with issues as they view the trial sometimes as a better or new treatment being provided to them. Women participants also spoke about the gender norms and its role in their decision-making.

“During the consent-taking procedure, my husband accompanied me.... 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” (CT participant, Gujarat).

Understanding of sociocultural contexts, resulting dynamics and ways to tackle them is important to facilitate a process of consent that is truly informed. Interviews with KIs revealed that some investigators and coordinators discussed the information with the participants and their families about the various aspects of the trials including other options available for the participants and helped them make a decision regarding participation in the trial.

“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” ([CT participant, Andhra Pradesh).

Ensuring participant signature on the informed consent form

All the participants in the study informed that they had signed the consent forms while enrolling in the study. However, as indicated above the factors influencing the decision-making process varied across the respondents and merely signing the consent cannot be considered indicative of the voluntariness in decision-making.

It was also found that informed consent was mainly administered by the Clinical Research Coordinator rather than the principle investigator. The lengthy consent forms, technical language used in the forms, and lack of agency of participants are major hindrances toward obtaining a truly informed consent. Sponsors expressed their inability to ensure that informed consent is taken in a proper manner as they are not directly involved in the process of consent.

On exploring the possibility of audiovisual (AV) recording of the consent with the KIs, their opinion was divided. Major concerns were regarding the privacy and confidentiality of the participants and the logistical issues associated with video recording consent for large trials.

AV recording of informed consent was made mandatory by the CDSCO as part of the amendment through which the process including imparting of the information and the participants understanding of the same has to be maintained in addition to the written informed consent.^[3]

While this was considered as a welcome move, there were concerns raised about the logistics of the AV recording and regarding the reluctance of participants in getting videotaped. A study among rural community regarding their willingness to be recorded during the consent process found that more than one-third of the participants refused to be videotaped due to lack of interest in AV recording or feeling shy in front of the camera.^[4] The rule was further amended in 2015, where it was clarified that AV recording was mandatory only for vulnerable participants in NCE trials. Further, only audio recording needs to be maintained of the informed consent process in case of anti-HIV or antileprosy drug trials.^[5]

Adverse events

One key component of trial is recognizing and reporting of adverse events (AEs). It was found that some of the trial participants were given a list of plausible adverse effects. Phone number of doctor was given for the participants to contact the doctor immediately on the occurrence of the AEs. The trial participants were expected to identify the AEs themselves and report it to the doctor.

It was found that some of the participants experienced dizziness, fever, headache, and pain in chest, whereas one of them developed a lump/swelling behind the ear. Some participants sought care from the local doctor for AEs that they perceived as minor without reporting them to the PI. This reiterates the need for informing participants about the significance of AE reporting and routine follow-ups. Further, since the AE is not recorded, the expenses incurred by the patient while availing treatment is also not reimbursed. The KIs lacked clarity on the timelines and processes of AE reporting. It also appeared that the AEs were recorded primarily to give a report to the sponsor, EC, Drug Controller General of India (DCGI), etc. If linkages were made properly, compensation also could be claimed and given appropriately to trial participants. It was seen that vast majority of the AEs were recorded as not linked to the trial and therefore no compensation was provided.

Compensation for injuries

The process of CT can lead to research-related injury for the participants ranging from minor harms to severe injuries. It was found that very few KIs were aware of the requirements in schedule Y,^[6] [under the essential elements of informed consent] or other regulatory guidelines (Indian Council of Medical Research [ICMR] Ethical Guidelines, Section 2.4.7 of GCP) regarding the provision of insurance and/or compensation for injuries during CTs. However, the study was undertaken in 2012 when the amendment regarding compensation for CT injuries was yet to come into effect. The amendment brought into effect a structured mechanism of AE reporting and compensation.

The KIs were mostly in favor of providing compensation to the participants in case of occurrence of any trial-related injury/death. Simultaneously, they raised some issues pertaining to compensation including paying compensation to terminally ill patients, participants of placebo trials, dropouts from CTs, etc.

Trial participants were found to be completely unaware of the provision for compensation in case of trial-related injuries. Interviews with participants also revealed that CT insurance is another aspect of which the participants are unaware.

“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” (CT participant, Andhra Pradesh).

It was found that PI, sponsor, and EC members played a major role in deciding the compensation amount. The quantum of compensation was arrived at based on a number of factors including the number of earning members in the family, number of dependents, number of children in the family, age

of the participant, his/her earning capacity, type of disease the participant is suffering from and the stage of the disease etc.

“Usually, the sponsor decides the amount of compensation. However, doctors assess the circumstances and calculate the amount accordingly. . . The compensation is usually decided by the EC 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” (CT participant, Gujarat).

The compensation mechanism for CT injuries has undergone many changes in the period following the study as reflected in the amendments to the rule 122 DAB in December 2014. The process of AE reporting and decision-making in compensation has been streamlined. Compensation formulae have been drafted to aid in the decision-making regarding the compensation amount.^[7]

Three independent expert committees have been constituted to look into the cases of SAEs of death and recommend DCGI on the matters of compensation.^[8] As per the information from the Ministry of Health and Family Welfare, 31 cases of deaths were paid compensation in the year 2013 and 22 in 2014.^[9]

While these are considered as steps in the right direction, experts have pointed out that many lacunae still exist within the system. The compensation formulae have been criticized by experts for the gaps in the same.^[10] Establishing the causality is the most significant challenge. In the absence of an assessment protocol, the committee members must exercise their collective expertise to reach a consensus, which might be influenced by their conflict of interests or biased based on the opinions of senior experts. They are also dependent on the reports provided by the sponsor and the investigator. Another criticism is the lack of space for the participants or their representatives to express their views and voices.^[11]

CONCLUSION

The years 2013–2015 saw multiple changes in the regulatory environment ranging from changes in the approval process and criteria for conducting CTs, informed consent process, registration of ECs, and compensation for CT-related injuries. ICMR is also in the process of revising the ethical guidelines for biomedical research to be abreast with the changed context in which trials are being conducted. However, the deliberations on CT regulations and upholding of participant rights need to be placed in the context of current clinical care setting in India.

Inequities in health, a debilitated and weakened public health system, high out of pocket expenditure, and lack of access to medicines are some of the structural issues. Combined with this, are the issues of information and power asymmetry, gender and sociocultural norms influencing the participant provider interactions, and decision-making processes.

Human research serves to advance medical science by understanding the safety and effectiveness of medicines. Without volunteers, healthy and those with some disease condition, this process would be impossible. However, the participants in CTs are often unseen, invisible, who are unaware of their rights. It is imperative that human participants are protected from unnecessary and avoidable harm, their rights are protected, and trials are conducted in an ethical manner. The right to life, right to health, right to autonomy, right to privacy, confidentiality, enjoyment of the highest available standard of physical and mental health, etc., should be the underlying principles respecting human rights while conducting trials.

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Conflicts of interest

There are no conflicts of interest.

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