

Ethical issues in recruitment of “healthy volunteers”: study of a clinical research organisation in Hyderabad.

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Abstract

This paper raises some of the ethical issues involved in the recruitment of healthy volunteers (HVs) by clinical research organizations (CROs) for bioavailability and bioequivalent (BA/BE) studies. It also explores the underlying reasons for the participation of the HVs and their interaction with the CROs. The findings are based on the data collected from 50 HVs participating in a BA/BE study conducted by a CRO in Hyderabad and from the key officials involved in it. The findings indicate the existence of various complex networks, throw some light on the role of middlemen (“Anna”) and the negotiation process, and give us an insight into the social norms and values that compelled the HVs to participate in the study. The paper offers a critical analysis of a few ethical concerns.

Introduction

The rising cost of medicines has been one of the important factors that have contributed to the overall health expenditure across nations. Finding generic equivalents of brand name drugs has always been the strategy for reducing the cost of medicines. As a consequence, the number of bioavailability and bioequivalent (BA/BE) studies aimed at obtaining approval of generic equivalents of branded drugs is on the rise (1). HVs required for BA/BE studies are recruited by the clinical research organisations (CROs), but the regulatory mechanisms are quite inadequate. The Drugs Controller General of India (DCGI) is trying to make it mandatory for BA/BE studies to be registered with the Clinical Trial Registry of India (CTRI). However, this is yet to become a reality as the National Institute of Medical Statistics (NIMS) has expressed its inability to cope with the work pressure, given the fact that it does not have enough scientists or funding to launch the project (2).

CROs (also called contract research organisations) are an integral part of the overall biomedical economy and are usually private, for-profit service providers. Their sole purpose is to conduct trials for pharmaceutical companies. Kaushik Rajan (3) states that CROs are a major force to reckon with within the clinical trial industry. This, in fact, indirectly influences the regulatory framework in many ways, weakening it and creating scope for ethical violations. The present paper examines the intricate relationship between CROs and HVs, and also, the process of the recruitment of HVs.

Methodology

We carried out a case study of XYZ (a pseudonym for a CRO) to gain a deeper understanding of the factors underlying

the participation of HVs in trials. XYZ is a sister firm of a pharmaceutical company. Their therapeutic targets include AIDS, allergies, Alzheimer disease, arthritis, asthma, cancer, diabetes, pain, pediatric illnesses, reproductive health, stroke, and cardiovascular, dermatological, urological, orthopedic, respiratory and neurological problems. The infrastructure of XYZ and its facilities and level of hygiene are comparable to the high standards maintained in a corporate office. XYZ is engaged in facilitating clinical trials and conducts BA/BE studies. It has conducted over 200 BA/BE studies, as well as several phase II and III trials to date. This CRO is well equipped and can accommodate more than 500 volunteers. After an initial rapport-building session, eight key officials [vice president, manager of the clinical unit, three principal investigators, public relations officer, voluntary mobilisation team’s [VMT] manager and coordinator] were interviewed in depth. A group discussion was held with 50 HVs (all men, who were residing in the CRO for 15 days) who were participating in a BA/BE study. In addition, we observed 40 volunteers (men who were observed but not interviewed) in the CRO premises who were participating in the informed consent form (ICF) session. The present research study was conducted over seven days during office hours.

The researchers submitted all the required documents, including the proposal to the CRO from time to time, explaining the purpose of the study. However, obtaining the CRO’s permission proved to be a challenging task. It was only after five months of repeated requests to the CRO that we were finally permitted to conduct the study, that too, within a short period of time. Once permission had been granted, the researchers took great care to explain the purpose of the study and obtained an oral consent from the HVs. In order to protect confidentiality, the names of the respondents and the CRO have not been disclosed.

The recruitment process

The VMT mobilises and recruits HVs from different sources, such as shanty towns (*bastis*), NGOs, hostels, villages and colleges. The VMT’s manager says:

Over a period, we have developed a network wherein we need not put in the same effort as before to procure the subjects [the term used by the scientific community for HVs]. We now have a list of subjects who would participate in BA/BE studies whenever intimation is sent as we have developed a good rapport.

Once the HVs have been recruited to participate in a study, they are counseled and screened, and the implications of the study are explained before their written consent is obtained on the ICF. After signing the ICF, the HVs are supposed to submit all their credentials, such as the birth certificate, voter ID and ration card. They must also undergo a complete health check-up, starting from basic blood and urine tests to an ECG and enzyme-linked immunosorbent assay (ELISA). This is necessary so that the CRO can confirm whether the potential volunteers are healthy or not. The volunteers are chosen on the basis of the inclusion and exclusion criteria of the study. A CRO screens considerably more people than are required for the study because not everyone who is screened will be deemed healthy enough to enrol himself/herself in the study. The HVs are paid an amount of Rs 200–500 for having themselves screened, according to the VMT coordinator. All HVs who are screened are paid regardless of whether or not they are selected. After the ICF session and screening, the HVs are selected for participation in the study.

Once the HVs are enrolled in a study, they are constantly under the medical gaze¹. The HVs are known by code numbers, and their names and details are kept confidential. The research coordinators document the study. Individual data is documented meticulously. Biostatisticians analyse the markers of the pharmaco-dynamics and kinetics of the drug and then submit their report.

S. No.	Occupation	No. of HVs	Education
1	Laboratory assistants in a pharmaceutical company	7	Diploma
2	School teachers	2	Graduation
3	Salespersons	4	Higher secondary
4	Security guards	5	Higher secondary
5	Painters, plumbers, masons, electricians, mechanics	15	Secondary
6	Tea stall owners	5	Primary
7	Housekeepers in hotels	6	Secondary
8	Gardeners in companies	4	Primary
9	Unemployed	2	Higher secondary
Total		50	

Healthy volunteers

A group discussion was held with 50 HVs. The age of the HVs participating in the BA/BE study ranged from 18 to 46 years. Of the 50 HVs, 64% had studied up to higher secondary level, 14% were diploma-holders (technical), 18% had completed only primary school and the remaining 4% were graduates. Their occupations were diverse. They included laboratory assistants, painters, plumbers, salespersons, electricians, field technicians, mechanics, security guards, helpers, tea stall

owners and housekeepers. Two were school teachers and two were unemployed. The group discussions with all 50 volunteers were held on the same day. All of them wore a uniform provided by the CRO. The day on which they were interviewed corresponded to the third day of the trial. Table 1 presents the profiles of the HVs.

The profile of the HVs indicates that all 50 participants belonged to the low-income group, mostly to the unorganised sector. One can see that their decision to become HVs was driven by several types of constraints, particularly financial. Initially, they gave the impression that they participated in the trials for the “larger good” of society. When probed further, they revealed that they had chosen to participate in the trials due to insufficient income and unstable jobs. They believed that they would receive better remuneration in the CROs. The remuneration is based on the risks involved and the number of days the HV stays in the CRO. One of the respondents, a laboratory assistant in a pharmaceutical company, said:

My job is based on a contract. The company pays me Rs 7000 per month, while the clinical research organization pays me around Rs 10,000, with all the other facilities.

None of the 50 HVs knew anything about the study in which they were participating. It was surprising that even the volunteers who were graduates did not remember any of the details of the trial (the name or purpose of the study). They only remembered that blood would be drawn from them, that they may develop rashes or a headache, and that they should report any other symptoms that crop up. They were quite confident that the doctors and the facilities available would suffice to deal with any health risk they might encounter in the course of the trial. Several HVs said that participating in these studies was like an alternative profession for them.

During the ICF session² it was noted that the volunteers were more concerned about the issue of payment than their health. The amount mentioned or agreed upon in the protocol document does not match the amount paid to the volunteers. While the ethics committee laid down that the HVs are paid Rs 2500, the VMT coordinators promised Rs 5000, but the HVs demanded Rs 10,000. It was finally negotiated that the HVs would be paid Rs 8200 for seven days, in addition to allowance for travel, accommodation and food. It was observed during the ICF session that there were good relations between the HVs and officials. This is one of the ways in which a CRO attempts to retain its pool of volunteers. If it maintains good relations with the HVs, the latter are more likely to be available whenever they are called for. The CROs have thus created a “reserve army” of HVs.

The group discussion revealed that the HVs participate in trials frequently. Table 2 shows the frequency of volunteering serially, and it can be seen that on an average, one HV has volunteered for at least five studies.

Table 2

Distribution of HVs by frequency of volunteering

Number of HVs (%)		Frequency of volunteering
9	(18)	1
6	(12)	2
3	(6)	3
8	(16)	4
5	(10)	5
2	(4)	8
5	(10)	9
8	(16)	10
4	(8)	11
Total	50 (100)	Average number of times volunteered: 5.13

The table shows that the HVs have been participating in BA/BE studies repeatedly, subjecting themselves to trials “voluntarily.” Except for the nine volunteers who were participating for the first time, the rest had participated more than once. The volunteers had also participated in the trials of other CROs in Hyderabad, Bangalore, Pune and Chennai. The data show that HVs participate in trial after trial so as to earn a living or supplement their meagre incomes. Just as the CROs establish networks to gather a pool of volunteers, the HVs establish their own networks to receive information about trials. They have colleagues or friends who share such information with them and sometimes, they also pool in volunteers themselves, making the CROs’ job easier. An HV who was participating for the first time said:

I got to know about the trials through my friends. Initially, I was apprehensive, but after hearing that nothing happened to them, I also joined them.

With the help of the “network” they have formed among themselves, the volunteers have established themselves as potential participants and, therefore, they would be called when required for a trial, whether in Hyderabad, Bengaluru, Pune, or Chennai.

Another HV, who was participating for the eleventh time, said:

We get to know of the trials as all the CROs in Hyderabad, Bengaluru, Pune and Chennai have our contact numbers. They contact us when required. Or else we have a brother, “Anna”, who would inform us and we would join.... “Anna” is the common friend of the CROs and us. The CROs contact him first and then he pools us together, while a few CROs call us directly.

“Anna” also negotiates between the HVs and the CRO, whenever the former file a complaint against the CRO in the police station for not making the due payment. The CRO has a public relations department which looks into complaints lodged by the volunteers. The VMT coordinator says:

The complaints are not filed as first information reports. They are resolved mutually between the parties and a bribe is paid to the local police.

The HVs revealed that they had lodged a complaint with a view to receiving higher remuneration from the CRO and that their intention was not to create any problems. The study respondents also said that they could not afford to fight with the CROs. However, the study respondents felt somewhat assured because the CROs fear the media and human rights organisations and hence, tend to accommodate some of their demands. One of the HVs, who was participating in a trial for the eighth time, said:

Sometimes we demand more money than what was agreed upon because a few of us developed severe rashes during the trials. When we questioned the officials as to why we were not informed, they did not have proper answers. So, we demanded more money. The CRO agreed to pay during the trial, but when the trial was over, they refused to pay, so we filed a complaint.

Ethical dilemmas and social values: some key issues

Recruitment: Although the ethics committee fixes the remuneration on the basis of the type of study, the commuting distance and other factors, HVs bargain for a higher amount than had initially been offered by the CRO. Subsequently, the CRO persuades the sponsor to pay the additional money, thus violating the ethical guidelines. According to the VMT coordinator, a volunteer earns anything between Rs 3000 and Rs 15,000, depending on the requirements of the study, and could take part in three trials a year. The coordinator said that even if the HVs participate in one study every three months, they earn money the rest of the year by participating in screening tests for other CROs.

According to the ethical guidelines for biomedical research (4), no volunteer can participate in more than one study every three months. However, the VMT coordinator revealed that there were instances of HVs offering their services several times, thus forcing the CROs to develop a bar coding system for the identification of the HVs’ fingerprints. However, not all CROs have this system, which means that many HVs participate in more than the stipulated number of trials.

During the ICF session, it was observed that the HVs were concerned only about monetary incentives. There was no discussion on the effect of the drug on their health. There was a great deal of bargaining between the VMT and the HVs. The latter were issuing mild and subtle threats that they may not join or might quit if they were not paid higher incentives. In fact, there was an argument in which the HVs pointed out to the VMT that higher incentives were being offered in Bengaluru and Pune than in Hyderabad.

According to the protocol for BA/BE studies and the biomedical research guidelines (4), if the participants are illiterate, they should be accompanied by an impartial witness. For this, a separate registry, called the impartial registry, needs to be maintained. However, it was observed during the ICF session that the HVs who had agreed to participate were not accompanied by anybody.

Healthy volunteers: The HVs had already decided to give their consent to participation in the study prior to the ICF session and, therefore, the session appeared to be a mere formality. This was, in fact, confirmed during our discussion with the VMT manager, who indicated that most HVs decide to participate before visiting the study centers or even seeing the consent forms. The role played by "Anna", who acts as a middleman/ intermediary or an agent for the CROs and HVs, gives rise to several ethical concerns. He is paid a commission by the CROs to help form a pool of HVs. The activities of these external parties must be taken into account by the regulatory authorities.

Another important issue is that of the ethical dilemma faced by the HVs. Except for the two school teachers, none of the others had informed their family members that they were participating in the study. The study respondents said that if they had told their family members, they would not have agreed and their kin and kith would have looked down on them. One of the HVs said:

Donating blood enhances our prestige, whereas if we subject our body to trials, people consider us very cheap and greedy, and they would look down on us and treat us as outcast. People would say that we are selling our bodies like prostitutes for the sake of making money.

These are the social norms which volunteers have to struggle against and this gives rise to certain ethical dilemmas. HVs resolve these dilemmas by subjecting their bodies to clinical trials clandestinely, keeping their participation a secret from their family or community members. On the one hand, they feel empowered by the fact that they have been able to make a "rational choice", i.e. participating in a study to supplement the family's income. On the other, they are "disempowered" or constrained by "social norms", according to which some of their choices are valued negatively and also stigmatised in Indian society.

Discussion

The data on poverty across the country indicate that about 836 million people live on less than Rs 20 a day (5). Poverty compels many to enrol in clinical trials as a way to make a living. The majority of the workforce is in the unorganised sector and it is sheer monetary compulsions that force them to participate in these studies. It is this context which leads HVs to provide consent even before the ICF sessions. The ICF sessions are just a routine matter for the HVs, whose participation in these sessions is passive. The sole point of interest for them is negotiating the remuneration for their participation. Adriana Petryna remarks that the phenomenal growth in global pharmaceutical sales and the quest for innovation are driving an unprecedented search for human volunteers, particularly in middle- and low-income countries. Medical progress increasingly depends on the willingness of the world's poor to participate in clinical drug trials (6).

Fisher points out that the neo-liberal state and its decreased commitment to health, education, employment and wages

have pushed people to the margins. Experimental trials are perceived of as "choices" and "opportunities" rather than exploitation or dependency, though one may say that the pharmaceutical industry makes enormous profits from the existing social and economic inequalities (7). As far as the concept of medical neo-liberalism goes, HVs are consumers in the context of capital-intensive scientific experimental trials.

The role of the state, particularly its regulatory leniency with the medical industry, has made it possible for clinical trials to draw heavily on the less educated, less skilled and marginalised class and caste groups. The irony is that the systematic use of economically disenfranchised people like HVs in pharmaceutical clinical development is not seen as being exploitative, but is instead presented as an opportunity for the members of these groups (7). This framework tries to provide an explanation about the ethical dilemmas individuals face in the current neo-liberal capitalist phase.

It is important to have an efficient regulatory mechanism to overcome these ethical issues. Though the 59th report of the Standing Committee on Health and Family Welfare (8) on the functioning of the Central Drugs Standard Control Organisation (CDSCO) recommends certain measures to do away with various violations, it does not address the root cause of the problem. Regulation of the recruitment procedures of volunteers should also be considered. Provisions should be made for auditing ongoing trials rather than merely examining the documents.

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Notes

- ¹ Michel Foucault, a French philosopher, coined the term "medical gaze" to indicate the medical separation of the body from the person/identity. For more details, see Michel Foucault's *The Birth of the Clinic: An Archaeology of Medical Perception*, 1973.
- ² The volunteers participating in the ICF session were different from the 50 who were already participating in the study. This analysis is based on the HVs' conversation with the VMT members during the ICF session.
- ³ "Anna" is the Telugu word for elder brother. In south India, particularly Andhra Pradesh, this word is used to refer to any adult male held in respect, whether or not he is a blood relation.

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Health equity for internal migrant labourers in India: an ethical perspective

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Abstract

In the developing countries, internal migration is a survival strategy for many labourers in search of a better livelihood and opportunities. It is inevitable that many of them will leave their home towns and villages in the coming years, and that the future will see an increase in the number of migrant labourers in developing countries such as India. Migrant workers face unique health problems and it is important for the health system to prepare itself to face these. In this context, the system will need to address certain key ethical issues. There is plenty of published literature on international migration and its ethical aspects. However, there is a scarcity of information on ethical issues relating to internal migration. This article examines these issues in the context of India. It addresses the issues of equity, non-discrimination, the provision of culturally competent care to migrants, allocation of scarce resources, and achieving a balance between benefits and risks for migrants. Our analysis should be considered while planning any healthcare intervention for internal migrant workers in all developing countries.

Introduction

Situation of internal migrant labourers in India

Historically and culturally, internal migration as a coping strategy for earning a livelihood has been a pronounced trend in the entire world. There is ample evidence of both voluntary and forced migration, which may result from cultural and religious persecution, natural disasters, developmental projects such as dams, a failed monsoon and the consequent famine, and the search for better livelihood options (1). Poverty and indebtedness are the most important factors that lead to migration. Workers migrating within a country usually move from less developed regions to more developed ones. In India, there are significant inequities in the development of the various states, with states such as Kerala, Tamil Nadu, Gujarat and Maharashtra having attained a higher level of development than Uttar Pradesh, Bihar, Jharkhand and

Chhattisgarh (2). Thus people move from the underdeveloped to the developed states. The total number of migrants as per the census of 1971 was 167 million. This rose to 213 million in 1981, 232 million in 1991 and 315 million in 2001. The figure was revised to about 400 million in 2004-5 (3).

Some scholars argue that the actual number has been grossly underestimated. They claim that the census and National Sample Surveys do not capture short-term migration, rural-rural migration, and women's migration for non-marital reasons and trafficking, all of which contribute significantly to migration (4). The insufficiency of data on internal migration is typical of most developing countries and does not allow one to appreciate the true magnitude of the issue. Migrant labourers, who account for roughly one-third of India's population, form a special group as far as the delivery of healthcare is concerned. Internal migrants the world over remain on the fringes of society. They work long hours, are paid low wages and work in unsafe environments, besides the other ills of social isolation and poor access to basic services, such as education, water, sanitation and health (5). This paper focuses mainly on unskilled and semi-skilled migrant labourers who migrate from low-income states to higher-income states in India.

Social determinants of health among migrant labourers

As mentioned in the introductory paragraph, the main reasons for internal migration in India are poverty and indebtedness. Labourers migrate from the underdeveloped states to the more developed ones to find work to fight poverty and indebtedness. Poverty is a universal determinant of health among most migrant workers, strongly influencing their health status. It is associated with malnutrition, a poor overall health status, poor access to preventive and curative health services, and higher mortality and morbidity rates (5). This determinant remains unchanged despite the migrant workers' relocation to greener pastures. Sometimes, the reason for migration