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The ethics of volunteer selection and compensation in Controlled Human Infection Models in India

ANURADHA ROSE

Abstract

Controlled human infection model studies, or challenge studies, involve the intentional infection of a consenting healthy human volunteer with a virulent organism under controlled conditions Such studies differ from clinical trials in that though both involve healthy volunteers, in challenge studies the potential harm experienced by participants is intended, not merely potentially foreseen, as in clinical trials. Given the special nature of CHIM studies, careful consideration of participant selection and compensation is essential. This paper explores the ethical criteria for recruiting participants in such studies, their own possible motivation such as monetary payment or access to treatment and how that should not amount to an inducement. It also distinguishes between compensation as inducement and fair compensation for the possible contracting of an illness, isolation, loss of work and adverse effects, and indicates that more research on the subject needs to be done.

Background

Controlled human infection model (CHIM) studies (or challenge studies) involve the intentional infection of a consenting healthy human volunteer with a virulent organism under controlled conditions. CHIM studies differ from clinical trials in some important aspects. While healthy volunteers are recruited for participation in both phase 1 clinical trials and challenge studies, the anticipation of harms is different. In challenge studies potential harm experienced by participants is intended, not merely potentially foreseen, as in clinical trials that evaluate safety (1). The first report from participants in a malaria human challenge model in Kenya found that participants reported financial compensation as their major motivator for participation (2), which emphasises the special nature of ethical review and oversight of CHIM studies, requiring careful consideration of participant selection and compensation. However, the objectives of ethical review and oversight remain the same, and they are to ensure the wellbeing and prevention of exploitation of research participants (3).

The memories of unethical research from the Nazi regime and other historical research where participants have been exploited have made some of the public suspicious of any type of medical research (4, 5). These violations of ethics have made medical research the object of close scrutiny by the media, public and regulators, with violations paving the way for the development of guidelines, codes and regulations governing the conduct of research. However, even though CHIM studies have been conducted for several decades now outside of India, until recently there have been no ethical guidelines developed specifically for this type of research.

In spite of the existence and use of guidelines, and scrutiny of studies by institutional review boards (IRBs), research has not been without controversies in India. Deviations from guidelines, both old and new, continue to make media headlines. In the light of this milieu, how can researchers ensure ethical conduct of CHIM studies, whose very design has the potential to arouse negative public opinion and media attention?

An important ethical violation often highlighted is the criteria used for selection of participants in research. Critiques have pointed out several deviations from ethical selection including deception during recruitment (5), poor consenting processes, and inadequate disclosure of risks, incentives and compensation clouding a potential participant's judgement, subtle coercion, vulnerable participants being chosen for ease of conducting the study and to ensure consent (6) and so on. Inadequate knowledge of participants' motivation to

Author: **Anuradha Rose** (anurose@cmcvellore.ac.in), Professor, Department of Community Medicine, Christian Medical College, Vellore, Tamil Nadu 632 002 INDIA.

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participate may result in a large proportion of people from lower socio-economic strata, "professional trial participants" participating in studies that require healthy volunteers, leading to criticism of exploitation. This can be avoided if there is good assessment of motivation to participate, strict criteria for the enrollment of participants and a clear justification of any compensation given.

Motivation to participate

In an ideal world, participants should be in a research study solely for the knowledge they can contribute, with altruism being the main motivator. Participation in research with no therapeutic benefits and very modest financial compensation suggests that people do participate for purely altruistic reasons (7). Carrera et al identify a form of altruism among research participants they have labelled "research altruism", where people participate in research if they feel it will help promote social benefit (7) However, literature also suggests that there are various, often complex, reasons to volunteer for studies (8). Reasons to participate seem to differ in phase 1 studies and in phase 3 studies, and between healthy volunteers and patient participants (9-12). The main motivators of clinical trial participants are financial gain, therapeutic options available in research projects, access to healthcare, contributing to science, and wanting to help find answers to medical issues, while barriers are mainly due to mistrust or fear of novel procedures (13-15).

In developing and developed countries, payment for participation and personal gain seem to be important motivating factors. But the profiles of participants who list monetary reasons as a motivator are different. In developing countries, they are mainly people from lower socio-economic groups, but in developed countries they are mainly from the younger age groups and students (12, 16,). Participants in a study in Brazil reported therapeutic option and financial compensation as the main motivators for their participation (17). In the same study, in the qualitative analysis, 94% of participants in a phase 1 study reported financial compensation as the main motivator, whereas in a phase 3 trial 100% reported therapeutic options as the main motivator. In a review of clinical trials by Grady et al, financial compensation was a major motivating factor though there were other motivators including altruism, healthcare benefits, scientific interest and interest in the goals of the study (10, 18).

In a qualitative study done in India, though 48% of participants reported personal benefits as a motivating factor, 43% gave contributing to the common good and altruism as the motivators for their participation (18). Trust in physicians was another important reason identified in this study, as well as participation as an extra source of income. Barriers to participation included mistrust in the organisation, concerns about confidentiality, dependence on others to make the decision to participate, and safety issues (19).

In a large study of healthy volunteers in phase 1 studies, risks, time, money, the competence and friendliness of research staff, and contributing to medical research were important factors influencing enrollment decisions for most participants (11). 70% of the participants in this study had previous research experience and many had low annual income and high rates of unemployment suggesting that financial gain was an important consideration. However, an important finding was that income levels did not influence perception of risk among these participants. Healthy volunteers considered risks as more important to their decision making than money paid for participating. Age, education and social status influence motivation for financial gain (16). However, another study suggested that increasing payment increases willingness to participate, irrespective of the risks involved (19). Participants with low income levels are more likely to be solely motivated by money, compared to those from higher income groups who list payment as one of many motivating factors (16). In developed countries, participants from younger age groups, mainly student volunteers, tend to be motivated solely by money (12). In another study involving 654 volunteers in phase 1 studies, participants were willing to take part in studies with familiar procedures and low risk, even though some procedures are painful, and these decisions were partially affected by payment (20).

Though many studies have been conducted to understand participants' reasons for volunteering, further research is needed as most current literature is from studies during the conduct of clinical trials or after they have been completed. There is a paucity of data on motivation to participate in CHIM studies, though this may be similar to reasons for healthy volunteers to participate in other early phase clinical trials.

Criteria for selection of participants

Research on motivation of healthy persons to volunteer in clinical trials suggest that there are several factors that influence their decision making, some of them may cloud judgement of risks (19). Stringent criteria for participation can select participants who are less likely to be exploited, with more altruistic motives for participating. Ethical guidelines, codes and regulations in current use have criteria for clinical trials (21). Participants should be:

- selected because they can provide answers to the scientific goals of the study and not because they are available or convenient to sample (22-24).
- from groups that will benefit from the results in the future (22, 23)
- the least vulnerable among the groups of people who could meet the scientific requirements of the study (24,25)
- excluded as a group of people on a scientific basis (25,26)
- selected from groups who benefit by the findings as they have borne the risks (27,28)
- excluded if they belong to groups who will predictably not benefit from the study (27, 28)

In addition to the above recommendations, CHIM studies, by nature of their design and risks, should have additional safeguards for selection. Participants should be able to understand the nature of the conduct of CHIM studies, the risks, the safeguards undertaken to protect them, and when to contact the study physician for side effects. In addition, it is necessary to discourage participation motivated purely by financial gain due to the tendency of such participants to ignore risks, as studies have shown (29).

Table 1 lists proposed criteria for participation in CHIM studies. These are proposed here for CHIM studies and may fairly be criticised as scientifically unsound and paternalistic. Nonetheless, for a country like India where perception often bypasses science, at least initially a paternalistic approach may be the best case to support the establishment of this form of clinical research for diseases of relevance to the country.

Justification for compensation

There is much debate on the ethics of payment of participants in research. Ethical issues rise when payment is seen as an inducement, sometimes at the expense of judgement of the risks of research. The history of paying research participants is almost as old as research itself. In 1900, Walter Reed paid healthy volunteers $100 in gold to be bitten by mosquitoes infected with yellow fever, and another $100 if they were infected (29). Payment for participation is common, though the reasons and amounts may vary. IRBs recommend paying participants for the following reasons:

- To reimburse expenses due to participation such as travel, refreshments on participation days
- To compensate for wages lost for those paid on a daily basis such as daily wages labourers, taxi drivers;

Guidelines suggest that participants be compensated for expenses incurred. The CIOMS guidelines state that, "Subjects may be paid for inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation in research; they may also receive free medical services. However, the payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgement ("undue inducement")" (30).

Ethical concerns over payments are due to several reasons. Payment of participants leads to commodification of research, and makes the relationship between the researcher and participant akin to a business transaction (31,32). Payment of money can skew the selection process. Studies have shown that payment attracts participants from poorer sections of society, younger people, placing undue burdens of research risks on the poor or younger participants such as students. Payment can be a strong motivating factor and inducement to participate, sometimes at the cost of negating risks (20).

Grady and Dickert suggest three models for paying research participants (32). The Market model pays incentives to facilitate participation, and allows escalation of payment to meet recruitment needs. The Wage payment model recommends payment for time, effort and uncomfortable procedures and

Table 1: Criteria for participating in CHIM studies

	Criteria	Justification	Criticism
1.	Participants should belong to the middle and higher socio-economic strata of society, so that the compensation offered by the study is not a significant incentive	Previous studies have shown financial gains to be a strong motivator for participating in studies (8, 17). The prospect of financial gain tends to cloud perception of risk (29). Because CHIM may be publicly perceived as experimentation on healthy individuals, including higher socio-economic strata prevents the perception of exploitation.	This might be seen as unfairly denying the poor the opportunity to participate. Researchers may be accused of being paternalistic. There is also no scientific justification for excluding poor but healthy participants.
2.	Participants should have a minimum educational qualification, possibly a degree or diploma	CHIM studies require deliberate infection of healthy volunteers, and their careful monitoring to diagnose and treat successful infection. Understanding the nature of the study, the risks and steps taken to ensure safety of volunteers is important for a valid consent. Educated participants can be tested in many ways to ensure understanding.	Discrimination due to poor education can be construed as paternalistic and unfair. Education and college degrees may not reflect health literacy and health related self-efficacy.
3.	Participants should have good access to healthcare	Studies show that many participants are motivated by therapeutic options, and this may also cloud judgement (9, 17,21).	In the absence of universal health cover in India, the health care offered through participation in the CHIM may be the only option for many people and this may be viewed as denial of possibility of good quality care.
4.	Participants should have similar goals to the researcher	Purely altruistic participants are rare, and research shows that motivation is often complex, with several factors being evaluated by participants. Participants who are altruistic, are willing to participate in the interests of science, or to seek answers for particular diseases should be recruited.	Motivation can only be assessed as stated by the participants

risks. The Reimbursement model recommends reimbursement for out-of-pocket expenses. The Wage model has the least potential to be an inducement and allows standardisation across studies.

Participants in clinical trials had different opinions on the role of money paid to them. Some thought it appropriate to be paid to compensate for time spent and discomforts experienced in research (33). Other suggestions were for payment to be proportional to time spent, number of procedures the participant had to undergo and severity or potential adverse events (34).

CHIM studies are subject to the same ethical concerns over payment of participants. In addition to the acceptable reasons to pay participants, such as in clinical trials, CHIM studies have certain other processes that might warrant additional compensation. Some studies require participants to be isolated during the period they may be infective to the community or for better monitoring of their physical health. This enforced isolation and its psychological and economic effects will have to be compensated. Participants who are successfully infected and who are allowed to go on to the disease stage may be compensated for the discomforts experienced by the illness itself and due to its treatment. This does not include compensation of any side effect or adverse event due to the study.

Table 2 provides the criteria used for compensation in clinical trials and those proposed for CHIM studies. Compensation may be monetary, but could also consist of recognition of altruism, provision of healthcare or other benefits. Discussions with potential participants in CHIM studies might be a way forward to decide the most appropriate form of compensation. Additionally, while CHIM studies rarely result in serious adverse events (3), planning for compensation in case of an adverse event will be a critical component of developing CHIM guidance and protocols.

Table 2: Suggested criteria for compensation

Compensation criteria	
Specific to clinical trials	Reimbursement of out of pocket expenses such as travel, refreshments Loss of wages, Costs for bystander including loss of wages
Additional criteria for CHIM studies	Isolation of participants Discomforts experienced due to research procedures Infection and illness and follow up

Conclusions

CHIM studies are different from other clinical trials and entail deliberate infection of healthy volunteers with virulent organisms. Careful selection of participants with stringent inclusion criteria is essential to avoid exploitation of participants vulnerable to temptation by payment, or who do not understand the peculiar nature of these studies. Compensation for participation is essential, but should be justifiable, with the rationale for payment explained by the researcher. Further research is needed to describe criteria for selection and payment of participants in CHIM studies, especially in the Indian context.

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Protecting challenge study participants in low and middle income settings

OLINDA TIMMS

Abstract

With India only just emerging out of a period of extreme concern and apprehension over clinical trials, the introduction of Controlled Human Infection Model (CHIM) studies calls for the need to proceed with caution, particularly with regard to protection of participants; especially vulnerable populations. In the Indian context, persons can be vulnerable due to circumstances of poverty, ignorance about clinical research and lack of access to education and healthcare. This paper will look at possible ways to provide protection to participants, starting with review and selection, through the trial period and after it is completed

Introduction

Since India is only just emerging out of a period of extreme concern and apprehension over clinical trials, the need to proceed with caution is crucial in the untested area of Controlled Human Infection Model (CHIM) studies, particularly with regard to protection of participants. The bitter lessons learned from the PATH-HPV vaccine trial in 2009 and the introspection that followed is still fresh in collective memory (1) and it needs to be shown how the learning from these and CHIM studies abroad can be incorporated into a contextual model that will respect the rights and autonomy of participants in human challenge studies, and provide them with all possible protection.

Author: **Olinda Timms** (olindatimms@gmail.com), Adjunct Faculty, Division of Health and Humanities, St Johns Research Institute, Bangalore 560 034, Karnataka, INDIA

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CHIM trials have only recently been attempted in low- and middle-income countries (LMIC) like India, mainly because this form of research requires rigorous review, quality-accredited and certified infrastructure, management protocols, and participant protection of a standard that may be difficult to achieve at reasonable cost, if not impossible. For these reasons, even regulated CHIM trials abroad do not have a long history and are mostly located in Western countries, with the analysis of related ethical issues available only since 2001 (2). Once convinced of the social and economic benefits of conducting such trials in India going forward, it will be incumbent on the scientific community and regulators to create an environment in which a viable, pragmatic model can be accepted.

Need for protection

One aspect is protection of participants in CHIM trials, particularly those who are vulnerable. In the Indian context, persons can be vulnerable due to their circumstances of poverty, ignorance about clinical research and lack of access to education and healthcare. The intervention of infecting human volunteers with disease-producing microbes in these studies places the responsibility on the scientific community to protect participants from undue harm, by limiting discomfort and ensuring thorough oversight. In light of this burden, it would be prudent to explore in advance, possible ways and means to protect future participants in these trials, starting with review and selection, through the trial period and after it is completed.

Review

Since the most recent Indian Council of Medical Research (ICMR) National Ethical Guidelines for Biomedical and Health