**Who should participate in CHIMs and how should they be compensated?**

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Controlled Human Infection Model (CHIM) studies differ from clinical research in two important aspects: The first is that healthy volunteers are recruited for participation, similar to phase 1 studies, and the second is that harms experienced by participants are intended, not merely foreseen (1 ). This changes the requirements for ethical review and oversight of CHIM studies. 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 (2).

The memories of unethical research from the nazi regime and other historical research where participants have been exploited have made the public suspicious of any type of medical research (3,4). These violations of ethical rules have made medical research the object of scrutiny by the media and public. Violations have also paved 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, there have been no guidelines developed specifically for this type of research.

In spite of the existence and use of various guidelines, and scrutiny of studies by IRB’s, research has not been without controversies. Deviations from existing guidelines, both old and new continue to make media headlines. In the light of this milieu of medical research, how can researchers ensure ethical conduct of CHIM studies , whose very design has the potential to cause negative public opinions 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 (4), poor consenting processes, inadequate disclosure of risks, incentives and compensation clouding potential participant’s judgement, subtle coercion, vulnerable participants being chosen for ease of conducting the study and to ensure consent (5) and so on. Inadequate knowledge of participants motivation to participate often results in a larger proportion of people from lower socio economic strata , “professional trial participants” and so on participating, leading to criticism of exploitation. This can be avoided if there is a good assessment of participants motivation to participate, strict criteria for the enrollment of participants and a clear justification of any compensation given.

**Motivation to participate**: Ideally, altruism should be the main motivator for a participant in a trial. However as literature suggests, there are various, often complex, reasons behind participants reasons to volunteer for studies (6 ). Reasons to participate seem to differ in phase 1 studies and in phase 3 studies, and again between healthy volunteers and patient participants (7-9). The main findings from research on clinical trial participants are motivation due to financial gain, therapeutic options available in research projects, access to health care, contributing to science, and wanting to help find answers to medical issues ; barriers are mainly due to mistrust in the institutions, or fear of the novel procedures and these are replicated in numerous studies (10-12).

In developing and developed countries, payment for participation and personal gain seem to me important motivating factors. But the profile of participants who list monetary reasons as a motivator are different; while they are mainly people from lower socio economic groups in developing countries, in developed countries they are mainly from the younger age groups and students (13,9 ). Participants in a study done in Brazil reported therapeutic option and financial compensation as the main motivators for their participation (14). In the same study, in the qualitative analysis, 94% of participants in a phase 1 study reported financial compensation as the main motivator, where as in a phase 3 trial 100% reported therapeutic options as the main motivator. In a review of clinical trials by Grady et al. financial motivation seemed to be the main motivating factor though there were other motivators including altruism, health care benefits, scientific interest and interest in the goals of the study(15,6). In a qualitative study done in India, though 48% of participants reported personal benefits as a motivating factor, 43% gave contributing to common good and altruism as the motivating factor for their participation (16). Trust in physicians was another important reason identified in this study, as well as participation for as extra source of income. Barriers to participate included mistrust in the organization concerns about confidentiality, dependency on others to make the decision to participate and safety issues (16). 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(8). 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 gains (13). However there are other studies that suggest that increasing payment, increases recruitment in risky studies (17). Monetary payments increase recruitment levels and willingness to participate irrespective of the risks involved (17). 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 (13). In developed countries participants from younger age groups, mainly student volunteers’ tend to be motivated solely by money (9). In another study involving 654 volunteers in phase 1 studies, participants were willing to take part in studies with familiar procedures and low risks, even though some procedures are painful, and these decisions are partially affected by payment.(18). Though many studies have been done to understand participants’ reasons for volunteering, further research is needed as most of the current studies are from studies during the conduct of clinical trials or after they have been completed. Also 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 clinical trials.

**Criteria for selection of participants:** Research on motivation of healthy persons to volunteer in research suggest that there are several factors that influence their decision making, some of them likely to cloud judgement on risks(16 ).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. These include :

- 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 (19-21).

- Participants should be from groups that will benefit from the results in the future (19, 20)

- Among the groups of people who could meet the scientific requirements of the study, the least vulnerable should be selected to participate (22)

- Exclusion of certain groups of people, women or children should have a scientific justification (22,23)

- Groups of people who bear the risks of research should also benefit from the findings (24,25)

- Groups who will predictably not benefit from the study should not be enrolled and exposed to the risks of the study (24, 25)

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 safe guards 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 previous studies have shown.

Criteria for participating in CHIM studies:

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|  | 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 (14, 6). The prospect of financial gain tends to cloud perception of risk (26). | This might be seen as unfairly denying the poor the opportunity to participate. Researchers may be accused of being paternalistic |
| 2. | Should be a degree or diploma holder. | CHIM studies, in order to answer the scientific question 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 for in many ways to ensure understanding. | Discrimination due to poor education can be construed as paternalistic and discriminatory. |
| 3. | Access to health care | Studies show that many participants are motivated by therapeutic options, and this may also cloud judgement (14,6,18). |  |
| 4. | Similar goals as 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 interest of science or to seek answers for particular diseases should be recruited. |  |
| 5. | Criteria for fair selection of participants from existing guidelines | | |

**Justification of 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 risks of research. The history of paying research participants is almost as old as research itself. Walter Reed paid healthy volunteers $100 in gold to be bitten by mosquitoes infected with yellow fever, and another $100 if they were infected (27). Payment for participant 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 etc;

-to compensate for wages lost for those paid on a daily basis such as daily wages laborers, taxi drivers etc.

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 judgment ("undue inducement")” (28).

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 (29). 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 (17).

Grady and Dickert suggest three models for paying research participants (30). 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 risks. The Reimbursement model recommends reimbursement for out of pocket expenses. The Wage model has the least potential to be an inducement and allows standardization 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 (31). 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 (32).

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.

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|  | 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 health volunteers with virulent organisms. Careful selection of participants with stringent inclusion criteria is essential to avoid exploitation of participants vulnerable to temptation by payments, 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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