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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.

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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

Research Involving Human Participants 2017 (3) do not contain any guidance for CHIM studies, a task force may need to create specific guidelines for this purpose, describing safety standards, review process, approvals and trial registration.

There could be multiple levels of review at ICMR, Drugs Controller General of India, Central Drugs Standard Control Organisation, state health departments and institute levels to ensure adequate oversight, at least in the early trials. Guidelines for CHIM studies should evoke standards that approximate those of a vaccine trial. Review and approval processes would go through the same rigor as with any clinical trial, focusing on researcher qualifications, provision of insurance and compensation by sponsor, schedule of interim reports, isolation facilities, and access to emergency treatment. Definition of "harm" and "risk" would be different in CHIM trials, and should be reviewed accordingly.

Selection

(i) Selection of microbe and vaccine

For the first CHIM trial it may be prudent to select, from among the range of infective agents that have local relevance and urgency, one that is of relatively short incubation time, having minimum predictable morbidity and well-established treatment. This could protect participants of early studies, while regulations and research protocols are further strengthened.

As immune response and symptoms of infection are expected observations in a CHIM study, these will not be listed as adverse events. Compensation mechanisms for unexpected reactions should be decided before the trial and approved by the ethics committee (EC). the clinical trials regulator needs to provide clarity on how challenge microbes are to be categorised, as they are neither drug nor vaccine. Challenge material should be defined in terms of strain, attenuation, dose and virulence and certified by an appropriate authority. All bio-safety standards should be met in production, storage, and handling of the microbe.

Of locally relevant challenge strains, only those strains that are quality-certified by good manufacturing practice (GMP) should be used. While this would be crucial in early trials where trust-building is important, this aspect of quality assurance (QA) would have to be a part of every CHIM trial going forward. Aside from protecting participants, it will build confidence in volunteers and in the scientific calibre of the trials, ensuring they meet their objective.

(ii) Selection of participants

Since only a small number of healthy volunteers is needed for CHIM trials, it presents the interesting possibility of preclusion of vulnerable populations, at least in early trials. For one thing, it would not be fair to unnecessarily burden a population that is socially or economically stressed, when participants from other segments are available. If the objective is to challenge persons drawn from a common gene pool, (eg South Indians), who are subject to similar pathogens and environment, this could theoretically be achieved without the inclusion of vulnerable groups. Unless the infectious disease affects only the vulnerable group, recruitment from the latter may be hard to justify. Even if a significantly altered immune response is apprehended due to nutritional status or disease burden, the vulnerable group could be included in later iterations, and need not be placed at the frontline of CHIM trials.

Socio-economic vulnerability in the Indian context refers to populations with inadequate access to adequate healthcare, increased susceptibility to coercion, and limited autonomy and capacity for informed consent. According to the WHO Expert Committee on regulatory considerations for Human Challenge Trials for Vaccine Development, "…accepting such risks requires absolutely that the elements of voluntary consent are based on truly being informed. It is for this reason (i.e. the need for truly informed consent) that consideration of conducting human challenge studies in children, or in any other vulnerable population, which would have diminished capacity to give informed consent, would not be deemed acceptable at this time." (4)

This may be a good opportunity to balance the scales and shrug off early disapprobation, when words like "victims" and "guinea-pigs" were used to castigate the clinical trials industry for prioritising the ends over the means (5). With a view to protecting vulnerable populations, they should be included only after CHIM trials have been managed satisfactorily with other volunteers. Since knowledge derived from CHIM trials will benefit all members of society, there is no reason why we should not bite the bullet and seek volunteers from among urban educated employed youth; not unlike volunteers for Phase I drug trials. In fact, there may be clear advantages.

The very nature of CHIM trials requires that potential volunteers are thoroughly informed about the unusual nature of the study, its importance and impact, counseled about the infection process, risk mitigation and treatment of disease, all the while allowing for clarifications and discussions. It requires a more astute awareness of science, health and rights, as CHIM trials directly cause infection; unlike drug trials that evaluate treatments. Volunteers could be sought from communities of youth, such as those found in tech-parks or work campuses. In such environments it is possible to conduct group discussions with volunteers, with detailed descriptions of the study format, risks and protection, ensuring that participants are fully informed before they consent. The level of awareness in such groups makes for better appreciation of the relevance and larger social benefit of such studies, appealing to human altruism.

The possibility of social contribution, and being a part of positive change may be motivating factors with this group; a form of positive peer pressure. These volunteers will not hesitate to demand all information, and transparency in the conduct of the trial. Employers could possibly be taken into confidence, briefed about the nature of the study, the need to support scientific research by sanctioning work-leave, even the suggestion that volunteers be acknowledged in some subtle way.

Work campuses could provide a conducive environment to advertise for volunteers, plan discussion events, and engage with employee needs. We can reasonably expect these volunteers to be unafraid to question, demand better conditions and protect their rights. Further, these work campuses usually comprise a reasonable representation from different parts of the country. Medical colleges are another option only because there would be better understanding about illness and research. The possibility of coercion cannot be overlooked here, but can be minimised.

Some drawbacks with recruiting educated youth on work campuses include that (a) it hinges on full support of the employer or company management, (b) peer pressure can work both ways and may have to be managed (c) in a competitive space, employees may not wish to jeopardise their career prospects d) health and nutrition levels in this group may be higher than country average and e) this cohort may be less tolerant of perceived injustice and may not hesitate to use litigation.

Informed consent process

Inability to evaluate the quality of consent in LMIC situations has always been a troubling aspect of research in these countries (6,7). CHIM trials present the opportunity to get the informed consent process right, especially if participants are educated employed urban youth.

There can be discussions on the work/college campus with volunteer groups that respond to the call for participation in the trial. Information about the microbe, disease cycle, discomfort and treatment can be described in details using print and video material. Once recruitment is finalised, Q and A sessions can be organised on the conduct of the trial, procedures, tests and blood draws, on-site accommodation, treatment protocols, and post-trial follow-up. Compensation for participation could also be disclosed at this time.

There should be clarity that once infected with the microbe, withdrawal from the study would neither be safe nor possible, and would have to be done as a planned process for welfare of the participant and others.

Depending on the microbe under study and its presence in the local environment, participants should be made aware of the need for confinement within the testing facility, and timeframes, until it is deemed safe to return to their families.

Counseling should be made available throughout the recruitment process and duration of the trial. Participants should be informed about the importance of complying with the follow-up schedule after the trial, including blood tests and scans.

The consenting process can be either individual or in groups, but every participant should have a copy of the patient information sheet, trial protocol, daily schedule and signed and witnessed consent form.

CHIM facility

A state of the art CHIM facility, designed and planned to house the participants during the trial, should be self-sufficient in terms of research equipment, offices, laboratories, medical treatment rooms and emergency care. Infective agents used in the CHIM trial should be securely stored and all waste treated as hazardous waste and carefully disposed. Rooms should be comfortable and well fitted out with furniture and en suite toilets. On site workspaces, internet connectivity, gyms, TV rooms and dining rooms would be needed. A clean well-maintained facility, adequately staffed with doctors, helpers, counselors and on-site treatment would reassure participants who may be apprehensive about getting infected. Participants should be insured against any possible adverse event during the trial, and all expenses of stay and meals during the study should be borne by the researcher/sponsor. The CHIM facility should be open to inspection by trial inspectors, regulators and EC members and systematic audit of processes and procedures should be in place.

Post-trial protection

Participants should be motivated to stay in contact with the research group even after the study, complying with the post-trial testing and check-up schedule. Health insurance cover should be provided to each participant for at least one year, and more if required. Any delayed response to the infection, or morbidity linked to the infection challenge, should be treated free of cost. Since the incubation time and disease pattern of the selected microbe in the first few trials would be reasonably well established, causality may not be much of a challenge in early CHIMs. Compensation as approved would be available for unexpected reactions to the microbe challenge. Participants should be provided with a health certificate and fitness certificate after the CHIM study to ensure there is no stigma or difficulty experienced in securing a job or social alliance. To protect against possible discrimination, appreciation certificates awarded by the Health Research Department can be considered, on completion of the study. Adequate public awareness programmes and social engagement in communities prior to recruitment can mitigate the possibility of stigma or discrimination. Participants should be provided information about the outcome of the study if they request it.

Conclusion

A feature of CHIM trials is that any benefit accrues largely to the wider society and not to the individual. A line from the touchstone document on research ethics, the Declaration of Helsinki, bears recall, "While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects."(8) Some degree of positive paternalism may therefore be justified, directed at protection of the participant, given the burden of responsibility placed on the doctor/researcher to minimise harm, while at the same time accepting that some harm may be deemed reasonable in relation to anticipated benefits. This balance of ethical

concerns (9) calls for heightened sensitivity and caution in design and execution of CHIM trials, even erring on the side of overprotection in the early trials lest we stumble at the starting post. The obvious benefits that may flow from such trials should inspire a concerted effort, drawing from our expertise and commitment to good research to create a durable model that could work for other LMIC regions as well.

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No previous submission.

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Law and ethics in consensual harm

VEENA JOHARI

Abstract

In recent times there has been an emerging interest in conducting Controlled Human Infection Model studies in low-and-middle-income countries, in which healthy human beings are infected with weakened pathogen strains under controlled conditions. These volunteers are monitored closely so that cures and prevention methods can be developed for the disease. Such studies call into question the legal sophistry of taking consent to harm a person by justifying it for the greater good or advancement of science. This paper analyses the law on the subject and the ethics of obtaining consent to harm another human being as in the context of Controlled Human Infection Models.

Introduction

Controlled Human Infection Model (CHIM) trials are conducted on healthy human beings, who are intentionally infected with a disease (the infectious organism could be close to wild-type pathogens, adapted or attenuated from wild-type, with less or no pathogenicity, or genetically modified in some manner) (1), in a controlled environment, so that science can trace the path of the infection, and what is happening at the molecular and cellular levels, and find the best time for medical intervention, develop a cure and/ or preventive methods against the infection (2). History has been marked by experiments similar to CHIM trials for diseases like small pox (3), dengue, malaria, influenza, tuberculosis, typhoid, etc. While the WHO guidance document states that it would be inappropriate to carry out CHIM trials for diseases that are virulent or even use an attenuated organism for those that have a high fatality rate, or a long uncertain period of latency, it does speak of the necessity for CHIM trials in a very few circumstances and the caution with which the trials should take place (1).

One justification often given for conducting CHIM trials is that they accelerate the development of vaccines or treatments, by using fewer financial and human resources than in clinical trials (4). But, can the use of fewer resources be enough of a justification to intentionally harm another human being? What about the obligations of the researcher "to do no harm" (non-maleficence) to research participants? Can we for the sake of the advancement of science harm healthy human beings? Such acts do, to some extent, violate Article 32 of the Universal Declaration on Bioethics and Human Rights that states "the interest and welfare of the individual should have priority over the sole interest of science or society" (5).

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