

THEME EDITORIAL

Controlled Human Infection Models: Exploring the landscape in India

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Introduction

Controlled Human Infection Models (CHIMs) refers to the intentional introduction of an infectious agent into a healthy volunteer to deliberately induce the infection under regulated conditions. These studies can be useful in discovering the origin and development of a disease, its immunological responses and natural course, as well as in the evaluation of interventions. CHIMs have yielded data that have informed the development process of several vaccines in recent years (1-5). Infectious diseases contribute substantially to the global burden of disease and therefore research and development in the context of infectious diseases is a high priority (6).

CHIMs are conducted on healthy volunteers, if found to be at least risk of harm after careful assessment. They are infected with a well characterised, highly attenuated, low virulence organism for which effective treatments are known and available, or those which produce only low grade, self-limiting illness. Moreover, they are carried out in well-regulated environments, which allow for close monitoring of the development of symptoms, easy access to effective treatment if needed, least risk for healthcare providers working in the facility, and least environmental hazards. Depending on the pathogen, the volunteers may also be isolated from the community for a defined period of infectivity of the pathogen, to avoid transmission of the disease to the community.

With the expanding interest in global health security against infectious diseases of pandemic concern, CHIMs have become an important part of the increasing thrust on vaccine development. Conducting CHIMs in low and middle-income countries (LMIC) where these infectious diseases are endemic could provide more relevant and appropriate results, particularly where prior exposure might influence the course of the disease or effects of intervention. Therefore, there is a growing discourse on increasing the capacity of LMICs to conduct CHIMs to tackle infectious diseases. There is need to explore the medical research landscape in India and assess the country's preparedness to conduct CHIMs.

Social value of CHIMs in India

Social value is one of the core and threshold elements in determining the ethical nature of a research activity (7). Obviously, the most ethically appropriate use of available resources would be that which has optimal social value. When social value is made a threshold criterion for assessing the ethics of a research study, it ensures justice as well as minimal exploitation of available resources. Research should simultaneously have scientific value, ie the potential to contribute to expanding knowledge in the area, and social value, to contribute to improvement in the society's quality of life. These two overlap but are not the same (8). Sometimes, scientific value is confused with social value, but all studies which have scientific value may not have social value. For example, a new vaccine or drug developed through research conducted in an LMIC may be potentially useful for global health, but if highly priced, it may never be accessible to poorer societies, though their people have shared the risks involved in evaluation of the drug/vaccine.

Therefore, some of the key social value considerations in the context of CHIMs in India, given the limited resources available, would be:

1. Who would decide on prioritising investment in CHIMs and developing new vaccines against infections vs research on treatment of diseases or research on other public health interventions such as safe drinking water, or environmental protection?
2. Will newer vaccines and medical products developed through CHIMs be accessible to the poor and needy in India?
3. Is the social value of CHIMs based only on anticipation of what "might happen," or is there enough pre-clinical, lab-based evidence of a greater social value? Pre-clinical studies and animal models help gain information about the pathogen and help

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better characterise it. Unless such a strong evidence base is available, such a CHIM cannot be said to be ethically sound. The NIH ethics panel which reviewed the CHIM on Zika articulated these points while deciding to disallow it (9).

CHIMs are a powerful tool for developing important public health interventions against infectious diseases. The scientific value of CHIMs has been demonstrated in examples such as typhoid vaccine, the efficacy of which was proved in a UK population unlikely to encounter the disease (2).

CHIMs are different from routine drug and vaccine trials

CHIMs are very different from other first-in-human experimental studies. Phase 1 clinical trials also introduce a new investigational product (a drug) into a healthy volunteer to study its biological functioning in the body. In that sense, they may be said to closely resemble CHIMs. However, the most important difference is that in Phase 1 drug trials, the drugs are intentionally given, also in a controlled environment, to individuals who will experience their effects and harms, if any. The drug will most likely be metabolised and excreted by the body, and thus only the person who takes the drug is affected. In CHIMs, the infecting organism is intentionally given to a person, who will experience its effect and harms, and this agent may have the potential to spread in the environment and infect others (eg in a malaria CHIM, the mosquitoes carrying the intentional malaria infection should not spread to the community and bite non-participants). While these are only risks that could be potentially harmful, their presence makes the consideration of ethical issues in CHIM studies potentially more burdensome than regular drug and vaccine trials.

The other important difference is that Phase 1 trials are intended to study and understand the way the drug works in the human body and its safety; whereas in CHIMs, the intention is to cause an infection. Though, the challenge agent used to cause the intentional infection is well characterised and attenuated, it is expected to cause infection or disease, however mild, and there is a risk of unanticipated serious disease.

Therefore, CHIMs constitute a very different and unique type of research and need special ethical consideration, ethical oversight, regulatory requirements and research governance. Discussions on CHIMs should necessarily include the prior setting up of such regulatory and governance frameworks as well as building the capacity to conduct and regulate, govern and oversee the CHIM studies.

Gaps in ethical frameworks for CHIMs: Emerging scholarship

The decision of the ethics panel of the National Institute of Health, United States, to disallow a Zika virus human challenge study for vaccine development, in early 2017, brought forth for discussion the wide gaps that exist in the ethical evaluation of CHIMs (9). The panel recommended:

"... Given the potentially devastating effects of Zika infection during pregnancy, the insidious nature of the disease, and the promise of what can be learned from human challenge trials, the writing committee concluded that a Zika virus human challenge trial could be ethically justified if certain conditions were met. However, at this point in time, based on what was heard at the consultation meeting and on our review of the latest scientific and ethics research, the writing committee has determined that these conditions preclude the conduct of a Zika virus human challenge trial, as detailed in the body of this report..."(9).

The panel also mentioned that "the literature provides limited guidance on the ethics of conducting [CHIM] studies when the medical consequences are more uncertain."

Some of the important gaps in the ethical frameworks for CHIMs are:

1. Intentional infection of volunteers however mild, poses issues of balance between defined and expected risks and uncertain benefits.
2. If a study uses an infective agent potentially bearing high risks, does this preclude the conduct of CHIMs? Or would appropriate precautions and mitigation measures make them permissible?
3. Clear definitions of harm and self-harm, even with the consent of the volunteer, will have to be developed and carefully scrutinised, from both legal and ethical perspectives. Where infectious diseases are concerned, conflict with legal provisions in some states/countries making actions that can lead to or worsen an infection punishable such as the Madras Public Health Act-should be avoided.
4. The issue of informed consent for undergoing harm becomes more problematic in LMICs where the levels of literacy and health awareness are likely to be variable and less than in the High-Income Countries (HICs).
5. Fairness in the recruitment of volunteers, considering their safety, vulnerability, avoidance of exploitation, and protection of their autonomy is a key issue.
6. Fairness in compensation for participation without it becoming an undue inducement, is especially important in LMICs.

Studies from HICs have shown that financial inducement is an important reason for volunteers to participate in trials (10). Inducement is unacceptable from a moral standpoint in both LMICs and HICs, with implications for the participants' autonomy. However, autonomy should not just be viewed as an absolute moral value. It must be seen from the perspective of whose autonomy is being influenced; who is influencing this autonomy; what the consequences are to that person of the compromised autonomy; and "whether the person has recourse to measures which will mitigate the compromise to autonomy. When viewed from this lens, inducement for participating in CHIMs becomes ethically more problematic in LMICs than in HICs.

7. Unique and effective methods of engagement with the public to create awareness about CHIMs, address anxieties and concerns-without creating negative publicity on the one hand, or overzealous claims of solutions to problems on the other is important.
8. Developing mechanisms for data sharing and knowledge sharing to avoid unnecessary duplication of effort and expenditure of resources, and help the scientific community to develop a rigorous framework for research.

Substantial scholarship has emerged over the past two decades on the ethics of CHIMs, and has addressed the concerns highlighted above (11, 12). However, there is still a need for discussion and debate on the ethical considerations of conducting CHIMs in India, and to develop a strong ethical framework for evaluation of CHIMs to be conducted in the country

Research ethics review, regulatory framework and governance in India

The Indian Council of Medical Research (ICMR) first made a policy decision to have ethics committees oversee clinical research in 1980. Since then the ethical review capacity has slowly increased in the country. We have the Ethical Guidance on Biomedical Research on Human Participants which was published by the ICMR in the year 2000, revised in 2006 and again in 2017. Schedule Y of the Drugs and Cosmetics Act which was proposed in 1988, and has been revised periodically requires the independent, impartial ethical review of all clinical trials involving drugs, medicines and biological products for use in humans. Several important limitations of the ethical review capacity of clinical trials in India including poor ethical review capacity, overemphasis on scientific review of proposals, infrequent ethics committee meetings, poor administrative support for the ethics committees, delays in approval, lack of participation of non-technical members in the committee, lack of declaration of conflicts of interest and lack of ongoing monitoring and review of outcomes and adverse events in clinical trials, have been discussed in the literature.(13).

Measures have been introduced to improve the capacity and functioning of the ethical oversight committees. The Forum for Ethics Review Committees in Asia-Pacific (FERCAP), under the Strategic Initiative for Developing Capacity in Ethical Review Recognition Program (SIDCER), started accrediting ethics review committees on a voluntary basis since 2002. The Forum for Ethics Review Committees in India also participated in this effort to strengthen ethics review committees. However, this process remains voluntary and not many ethics committees in India come under this accreditation umbrella (14). In 2013, registration of all ethics committees that review clinical trial protocols with the Central Drugs Standard Control Organisation (CDSCO) was made mandatory. The Clinical Trials Registry of India is yet another regulatory requirement, emphasised by CDSCO, to bring in research accountability and to meet global standards for research governance. While these measures have been helpful, much progress remains to be made.

Given this evolving research ethics review, regulatory and governance mechanism in India, the introduction of CHIMs needs to be closely evaluated. One perspective may be that the need to strengthen ethical review, regulatory and governance frameworks for CHIMs may accelerate the overall research review and governance framework in the country. The other perspective is one of deep concern, that a precipitous introduction of CHIMs may add an undue burden to the already struggling research governance mechanisms.

The birth of this theme issue and what it covers

In this context, a multi-stakeholder consultation meeting was organised by the Translational Health Science and Technology Institute of the Department of Biotechnology, working with the ICMR, at the Tata Institute of Social Sciences in Mumbai on January 7 and 8, 2018, to deliberate on the ethics of CHIMs in India. The stakeholders involved in the meeting were biomedical scientists, researchers, medical experts, clinical trial experts, ethics committee members, ethicists, social scientists, anthropologists, health communication experts and media personnel. This theme issue was born out of the discussions at the meeting. Some of the most important debates identified in the meeting were noted, and writers were invited to elaborate their points of view. This theme issue carries seven invited commentaries on various topics relevant to the ethics of CHIMs in LMICs, especially in India.

Selgelid and Jamrozik have presented a comprehensive overview of the ethics of conducting CHIMs, and the challenges that CHIMs produce in LMICs. They argue that CHIMs may not just be "permissible" in LMICs, but may be "required" under certain conditions. (15). Dholakia, in his interesting paper uses the "reflective equilibrium" approach and argues that vaccines are a "fundamental need" in the endemic LMIC countries and therefore conducting CHIMs in India is an ethical obligation, not a choice. (16)

Rose's paper presents measured arguments on the selection of volunteers to participate in CHIMs. She refers to financial gains being the greatest motivator for participation in clinical trials and expresses concern that the financial compensation may unduly induce volunteers to participate in CHIMs. She proposes interesting measures to prevent such inducement (17). In a close follow up to Rose's paper, Timms presents some important measures to protect the vulnerable participants in CHIMs (18).

Johari in her paper covering the legal issues relating to CHIMs, focuses on the concept of informed consent and raises the question "Can healthy individual volunteers consent to being harmed in order to advance scientific knowledge?" (19).

Vaz covers ethical issues related to CHIMs and argues for a strong community engagement in CHIMs as an ethical obligation (20). She also reflects on the appropriate model of public engagement in India. Finally, Srinivasan discusses the role of the media in public engagement with CHIMs in its complexities and important nuances (21).

These scholarly works will expand the discussion and discourse related to CHIMs in LMICs, especially in India. The discussions will inform policies related to conducting CHIMs in India and will lead the way for a robust ethical framework for evaluation of CHIMs in the near future.

References

- Chen WH, Cohen MB, Kirkpatrick BD, Brady RC, Galloway D, Gurwith M, Hall RH, Kessler RA, Lock M, Haney D, Lyon CE, Pasetti MF, Simon JK, Szabo F, Tennant S, Levine MM. Single dose live oral cholera vaccine CVD 103-HgR protects against human experimental infection with *Vibrio cholerae* O1 El Tor. *Clin Infect Dis*. 2016 Jun 1;62(11):1329–35.
- Jin C, Gibani MM, Moore M, Juel HB, Jones E, Meiring J, Harris V, Gardner J, Nebykova A, Kerridge SA, Hill J, Thomaidis-Brears H, Blohmke CJ, Yu LM, Angus B, Pollard AJ. Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of *Salmonella* Typhi: a randomised controlled, phase 2b trial. *Lancet*. 2017 Dec 2;390(10111):2472–80.
- Darton TC, Jones C, Blohmke CJ, Waddington CS, Zhou L, Peters A, Haworth K, Sie R, Green CA, Jeppesen CA, Moore M, Thompson BA, John T, Kingsley RA, Yu LM, Voysey M, Hindle Z, Lockhart S, Szein MB, Dougan G, Angus B, Levine MM, Pollard AJ. Using a human challenge model of infection to measure vaccine efficacy: a randomised, controlled trial comparing the typhoid vaccines M01ZH09 with placebo and Ty21a. *PLoS Negl Trop Dis*. 2016 Aug 17;10(8):e0004926.
- Stanisic DI, McCarthy JS, Good MF. Controlled human malaria infection: applications, advances, and challenges. *Infect Immun*. 2017 Dec 19;86(1):e00479-17.
- Hodgson SH, Ewer KJ, Bliss CM, Edwards NJ, Rampling T, Anagnostou NA, de Barra E, Havelock T, Bowyer G, Poulton ID, de Cassan S, Longley R, Illingworth JJ, Douglas AD, Mange PB, Collins KA, Roberts R, Gerry S, Berrie E, Moyle S, Colloca S, Cortese R, Sinden RE, Gilbert SC, Bejon P, Lawrie AM, Nicosia A, Faust SN, Hill AV. Evaluation of the efficacy of ChAd63-MVA vectored vaccines expressing circumsporozoite protein and ME-TRAP against controlled human malaria infection in malaria-naïve individuals. *J Infect Dis*. 2015 Apr 1;211(7):1076–86.
- Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, et al, GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016 Oct 8;388(10053):1545–1602.
- Emanuel EJ, Wendler D, Grady C. What Makes Clinical Research Ethical? *JAMA*. 2010 May 24-31;283(20):2701–11.
- Ganguli-Mitra A, Dove ES, Laurie GT, Taylor-Alexander S. Reconfiguring social value in health research through the lens of liminality. *Bioethics*. 2017 Feb;31(2):87–96.
- Shah SK, Kimmelman J, Drapkin Lyerly A, Fernandez Lynch H, McCutchan F, Miller FG, Palacios R, Pardo-Villamizar C, Zorilla C. Ethical considerations for Zika virus human challenge trials: Report & recommendations [Internet]. Rockville, Maryland: NIAID and WRAIR; 2017. Available from: <https://www.niaid.nih.gov/sites/default/files/EthicsZikaHumanChallengeStudiesReport2017.pdf%0A>
- Grady C, Bedarida G, Sinai N, Gregorio MA, Emanuel EJ. Motivations, enrollment decisions, and socio-demographic characteristics of healthy volunteers in phase 1 research. *Clin Trials*. 2017 Oct;14(5):526–36.
- Miller FG, Grady C. The ethical challenge of infection-inducing challenge Experiments. *Clin Infect Dis*. 2001 Oct 1;33(7):1028–33. doi:10.1086/322664
- Bamberg B, Selgelid M, Weijer C, Savulescu J, Pollard AJ. Ethical Criteria for Human Challenge Studies in Infectious Diseases. *Public Health Ethics*. 2016 Apr;9(1):92–103. doi: 10.1093/phe/phv026.
- Thatte UM, Bavdekar SB. Clinical research in India: great expectations? *J Postgrad Med India*; 2008 Oct-Dec;54(4):318–23.
- Thatte UM, Marathe PA. Ethics Committees in India: Past, present and future. *Perspect Clin Res*. 2017 Jan-Mar; 8(1):22–30.
- Selgelid MJ, Jamrozik E. Ethical challenges posed by human infection challenge studies in endemic settings. *Indian J Med Ethics*. 2018 Oct-Dec;3(4) NS:274-8.
- Dholakia SY. Conducting controlled human infection model studies in India is an ethical obligation. *Indian J Med Ethics*. 2018 Oct-Dec;3(4) NS:279-85.
- Rose A. Who should participate in CHIMs and how should they be compensated? *Indian J Med Ethics*. 2018 Oct-Dec;3(4) NS:285-9.
- Timms O. Protecting challenge study participants in low and middle income settings. *Indian J Med Ethics*. 2018 Oct-Dec;3(4) NS:289-92.
- Johari V. Law and ethics in consensual harm. *Indian J Med Ethics*. 2018 Oct-Dec;3(4) NS:292-6.
- Vaz M. Public engagement in the context of a CHIM study. *Indian J Med Ethics*. 2018 Oct-Dec;3(4) NS:296-300.
- Srinivasan S. Public communication about CHIMs: What is the role of the media? *Indian J Med Ethics*. 2018 Oct-Dec;3(4) NS:301-4.

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