

REPORTS

Consultations on human infection studies in India: Do people's voices really count?

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Introduction

The Controlled Human Infection Model or CHIM, sometimes described as a human challenge study, is a relatively specialised medical research technique. Researchers infect healthy participants with a weakened strain of a pathogen in a controlled setting, in order to learn more about the infection and the disease, or to develop new vaccines for that disease. Unlike in other human clinical trials, where participants face a risk of harm because of, for example, the drug's side effects, healthy participants in CHIM trials are *deliberately* harmed through infection — contrary to every principle and guideline of medical practice and research.

The practice of deliberate infection avowedly in the search for knowledge is not new. The best-known instance dates back to 1796, when the physician Edward Jenner infected a child with cowpox, collecting information that eventually led to the development of the smallpox vaccine (1).

There are some 155 CHIM studies across the world, of which the vast majority are being carried out in developed countries, most of these in the US, the UK, and the Netherlands with a few in Spain, Germany, Australia and Belgium. More recently, CHIM has been used in Mali, Kenya, Tanzania, Gabon, Colombia, Thailand and Equatorial Guinea. The US clinical trials registry clinicaltrials.gov lists CHIM studies for malaria (76), influenza (30), respiratory syncytial virus (12), norovirus (9), shigella (6), typhoid (5), campylobacter (4), tuberculosis (4), hookworm (2), and cholera, common cold, dengue, e-coli, streptococcus pneumoniae, schistosomiasis, and celiac disease (1 each).

Today, CHIM seems to be largely used for the purpose of speeding up the development of vaccines. The current vaccine development paradigm, in which vaccine candidates are tested

in real-life settings, takes a long time and a lot of money. As was stated at a recent consultation, CHIM could be a strategy to cut the time and costs to "bring the vaccine to market." CHIM studies have contributed to the development of a cholera vaccine licensed by the United States Food and Drugs Administration (1), a malaria vaccine licensed by the European Medicines Agency (1), and a typhoid vaccine pre-approved by the World Health Organisation (2), among other products.

A series of consultations

Since 2017, there has been talk of introducing CHIM studies in India. Three consultations, bringing together scientists, public health specialists, lawyers and ethicists to deliberate on the science and ethics of CHIM studies, have taken place. The meetings have been supported by the Translational Health Sciences and Technology Institute (THSTI), an autonomous institute of the division of the Indian government's department of biotechnology (DBT). The latest of these meetings was held in March 2019.

At the first meeting in Vellore in October 2017, on the possible introduction of human challenge trials in India, participants asked for transparency in the decision-making process, with consultations with stakeholders, extensive public engagement, and taking the public into confidence, before such studies are conducted here.

The January 2018 consultation in Mumbai included biomedical scientists, social scientists, medical professionals, industry representatives, media, lawyers, nongovernmental organisations, and those working on ethics. At this consultation, researchers from Kenya spoke on their experiences with CHIM for a malaria vaccine. A presentation was also made on whether CHIM could be used for Zika virus research. This was followed by small group discussions on CHIM from the perspectives of basic science, industry, ethics, regulation, social science and the media. The group presentations indicated that views were divided as to the value of this research method. While some felt CHIM was essential for developing new life-saving technologies, others had reservations on the focus on new vaccines as a public health intervention at the cost of other public health measures, and without, for example, addressing the problem of low coverage of existing vaccines. Some participants also pointed to the lack of clarity on issues such as whether it was possible to take consent to be harmed, and whether the regulatory structure in

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India would ensure proper review and monitoring to protect vulnerable participants. The media group flagged the history of unethical research in India. The minutes of this meeting have not been made public.

A collection of papers developed after this consultation was published in the October-December 2018 issue of the *Indian Journal of Medical Ethics*.

In December 2018, researchers from St John's Research Institute's department of Health and Humanities, at a meeting ahead of the World Congress on Bioethics in Bengaluru, reported on a THSTI-funded study of people's perceptions of CHIM. Researchers organised focus group discussions with a cross-section of people on whether they would be willing to be infected with a disease of some kind, as part of research. While the responses were varied, many expressed strong misgivings about participating in this type of trial. The study report was not available, but the meeting participants were informed that it would soon be submitted for publication.

The latest meeting was held in Bengaluru on March 6, 2019, organised by the St John's Research Institute's department of health and humanities with funding from THSTI. The approximately 30 participants came from departments of infectious disease, microbiology, clinical research, community health, public health, medicine, health and humanities, law, media, and ethics, from public and private institutions, and nongovernmental organisations, in Bengaluru, Chennai, Gurugram, Hyderabad, Mangaluru, Mumbai, Thiruvananthapuram and Vellore.

Meeting to consider specific CHIM scenarios

The meeting started with an introduction on CHIM – what it consists of, when it is used, and what is needed to conduct biomedical research using the human challenge model. One of the uses of CHIM is to evaluate potential vaccine candidates and “fast-track vaccine development.” The presenter stated that the ideal controlled human infection model would be one for a disease of public health importance, for which no animal model is available, which can be treated, and for which various steps– including the use of specialised high-tech facilities – can be taken to ensure that there is no harm to the participant or the community. Finally, CHIM would require “appropriate ethical guidelines and national guidelines to ensure participant safety”, “well trained researchers”, “trained ethics committees”, “public engagement and support”, and “well informed volunteers”.

The introduction also touched on ethical concerns such as how volunteers would be recruited, how their consent could be taken, how they could be compensated for their time without inducing them to join the trial, and what level of risk would be acceptable in CHIM. Ethical arguments were also presented in favour of CHIM, particularly in developing countries. Traditional vaccine research exposes people to ineffective vaccines, increases research costs and delays vaccine development, leaving people without vaccine coverage, or with ineffective

vaccines. Second, most CHIM studies so far have been conducted in rich countries for diseases that concerned people in poor countries. It was said more than once: “These countries took risks for us... we should find solutions to our own problems.”

Three scenarios, several concerns

The next speaker presented three detailed scenarios in which CHIM might be considered in India – to test vaccines for typhoid, malaria and chikungunya – after which groups were asked to spend about an hour deliberating on the information gaps in the scenario, the feasibility of the research, and ethical issues.

A few concerns stood out in group presentations and the discussions that followed.

First, questions were raised about the choice of diseases. Though the introductory presenter stated that the ideal CHIM would be one in which no animal model was available, it was clear that animal models have been used for all three diseases. At the same time, the specialist presenter acknowledged that there was no point in this particular group discussing a CHIM for chikungunya, as it has no treatment. One person also pointed out that malaria is so extensively researched that a human challenge study is not likely to produce substantial and critical information, other than to test a new vaccine.

Additional questions came up in the case of typhoid, for which there is already a vaccine. A participant argued that if the current vaccine was used widely enough, it would be sufficient to create herd immunity to typhoid despite its limited efficacy. Hence, there was no need for a new typhoid vaccine using CHIM. Separately, someone asked if the new vaccine would be tested against a placebo when a vaccine already existed.* Such testing would seem to violate national and international ethical guidelines that restrict the use of a placebo in research when an effective intervention exists.

At this meeting, too, opinions were divided on the use of CHIM in India – whether it was needed, whether the necessary regulatory structure was in place, and whether it could be conducted ethically. A number of participants expressed their reservations, but others viewed human challenge trials as both essential and inevitable in India.

Are human challenge trials in India a done deal?

Participants were informed at the start of the meeting that there were at present no confirmed plans to undertake human challenge studies in India. However, it is possible that CHIM trials will be introduced in India, possibly by the end of 2019.

In July 2018, the DBT-European Union sent out a call for proposals for collaborative research for an influenza vaccine using CHIM (3), with an April 2019 deadline and a decision by August 2019. A researcher from THSTI has put in a proposal for this, though a THSTI representative stated at the meeting that influenza is not the best choice for CHIM research. Apparently,

researchers' assurances that CHIM would be used only when essential should be taken with a pinch of salt.

If DBT's first CHIM trial will be on influenza, it is not clear why participants at the March meeting were asked to discuss typhoid, malaria and chikungunya, diseases with a completely different mode of transmission.

The DBT-EU call does not specify that the human challenge studies must be done in India, and it has been suggested that the THSTI proposal may have been submitted with the understanding that the CHIM trials could be done outside India. However, other steps seem to suggest that moves are being made to start such trials in India as soon as clearance is given.

For one, in November 2018, members of THSTI and of the Christian Medical College (CMC), Vellore visited the Oxford Vaccine Group's laboratory in the United Kingdom to learn about the facilities needed for conducting CHIM trials in India. The Oxford centre has carried out many CHIM trials, including one of a typhoid vaccine developed by Bharat Biotech with support from the Wellcome Trust and the Bill and Melinda Gates Foundation**.

Second, CMC is apparently working on building capacity to do "first in human trials" including upgrading facilities for waste treatment and containment. These facilities would also be needed for CHIM trials, "So that if and when they are allowed, they are prepared," a participant mentioned in a post-workshop conversation.

And finally, a proposal for typhoid research using CHIM is also being developed.

These are just some indications of organisations making preparations to use CHIM in India.

It seems that this controversial trial method is being introduced in India without proper stakeholder consultation, public engagement, transparency and accountability. So, we feel the need to flag some major concerns regarding the introduction of human challenge trials in India.

Who will regulate and how?

It is not clear how CHIM studies can be conducted legally in India as there is no regulatory framework in place for research that involves intentionally harming participants. The Drugs and Cosmetics Act, 1940, regulates drug trials towards the development and marketing approval of new drugs. It does not mention the use of biological agents for non-therapeutic purposes. The draft consent forms in the Rules do not mention consent for intentional harm. CHIM would also be contrary to the principles laid down in the Indian Good Clinical Practices for biomedical studies, and the Indian Council for Medical Research's guidelines on biomedical and health research involving human beings, which emphasise that in research on human beings, the interest of science should never take precedence over considerations related to the wellbeing of participants (4,5).

However, THSTI apparently feels that the current regulatory framework is sufficient. "There is risk in so many medical procedures and in research too," said a THSTI representative. "Organ donation carries a risk but we don't need a separate law to do organ transplant." This is an inappropriate comparison in many ways. Organ donation has a direct benefit to the recipient; it is framed as a completely altruistic act, and the donor may not claim compensation of any kind. And there is in fact a separate law regulating organ and tissue transplants.

Incidentally, it was learned at the meeting that CHIM could be used to take a vaccine directly for marketing approval, bypassing phase 3 trials, raising other ethical and regulatory questions. Is it possible that CHIM studies would allow researchers to skip animal studies altogether?

Some lessons of human challenge studies elsewhere

Even a very scrappy review of information on CHIM studies flags major concerns. First, there are reports of volunteers in both developed (6, 7) and developing (8) countries joining a CHIM trial for financial compensation or for access to healthcare.

Second, though human challenge studies are supposed to use an attenuated or weakened pathogen, with close monitoring and prompt treatment as soon as infection is detected, ensuring that participants do not experience serious harm, the reality can be somewhat different. There are reports of volunteers experiencing substantial harm in these experiments. For example, some volunteers in a study of schistosomiasis experienced months of severe headache and body pain (9). This was in the Netherlands which one imagines should have the best of systems to protect volunteers. Volunteers in influenza CHIM studies have recorded heart damage, and in human challenge studies of shigella and e-coli infections have reported instances of long-term adverse effects such as reactive arthritis and post-infectious irritable bowel syndrome (1). In a general discussion, at the Bengaluru meeting, on a volunteer in Oxford reporting severe symptoms of typhoid (7), one of the meeting participants commented that the volunteer had taken part in multiple human challenge trials. This is a matter for concern. The reason for a volunteer to enrol in multiple trials is likely to be the compensation offered, and it is worrisome that researchers seem to have ignored such multiple participation. The suggestion that there is a link between multiple CHIM participation and severity of symptoms also implies that participating in a CHIM trial increases one's risk of a heightened reaction to any consequent infection.

On a related note, a member of CMC's ethics committee who visited the Oxford centre noticed on reviewing some documents that as much as 1,000 ml of blood had been collected from each participant in a CHIM study. Blood donors are not allowed to donate more than 350 ml of blood following which they may not donate again for three months. This fact was not reflected in the study publication. The EC member mentioned this to illustrate that published reports may be

incomplete. Such grave misgivings regarding human challenge studies go unreported and are thus not found in published papers, a major cause for concern.

Though CHIM has been around for decades, there is no uniform reporting of serious injuries in CHIM across the world, let alone a central registry of all such injuries. Though few adverse events may have been reported, "The absence of standardised reporting of adverse events...hampers the meta-analysis of available safety data." (1). This means we do not even really know how many serious injuries have taken place in human challenge trials across the world.

The vaccine paradigm and its problems

Vaccine development seems to be the most common reason to conduct a human challenge study. But the focus on vaccines as the primary public health tool needs to be subjected to greater scrutiny. Vaccines are one of many health interventions which must be weighed along with other interventions such as clean drinking water, sanitation, vector control, nutrition, etc, which have multiple benefits –and are also the community's right, and the duty of the state to provide. One of the participants at the March meeting pointed out that decisions on the need for a vaccine require subject specialists, epidemiologists, health system experts, civil society organisations, and the people, the communities themselves. Such discussions have not been part of the framework of these consultations.

Lip service to consultations?

The message is clear: despite observing the niceties of discussions and community surveys, there is every sign that the government plans to ramp up vaccine research in India using human challenge studies, with the support of funding organisations and as part of an international collaborative effort. The meetings since November 2017 may have served only to gauge the public's views on CHIM and give the impression of genuine consultation.

The government of India seems to be committed to human challenge studies and THSTI, one of its autonomous institutions, is focused on undertaking such studies despite its assurances that they would be considered only after specific requirements were met.

There must be a *scientific* consensus, on the basis of *scientific* data, that the research question at hand is critically important, and CHIM is essential to answer that research question. And the recommendations of previous consultations must be followed: systematic public engagement, taking the public into confidence, transparency at every stage, addressing ethical and social concerns, and a clear regulatory framework specific to CHIM. The government needs to be open, transparent, and most importantly ethical in its dealings about CHIM trials.

Many participants at these meetings have cautioned that, for a variety of reasons, CHIM trials should not be conducted in India. The health infrastructural facilities are poor, potential trial participants are vulnerable, and the regulatory and ethical

framework is substandard and will not protect participants subjected to this particularly problematic research method. A participant at the March meeting stated that even if CHIM were a good method, the current climate is not a good one to use this technique.

Such cautions and caveats may not be heeded in the transnational race for undertaking human challenge studies for new vaccines.

Declaration: Sandhya Srinivasan and Veena Johari attended the Mumbai and Bengaluru meetings. Their travel and accommodation for the March 6 meeting in Bengaluru were provided by the organisers.

Notes

- * The recently approved cholera vaccine in the US was tested in human challenge trials against a placebo, rather than against other approved cholera vaccines, which seems to go against international ethical guidelines.

Correction

- ** This sentence was corrected at the authors' request on April 15, 2019. The error is regretted

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