Consultation on the feasibility and ethics of specific, probable Controlled Human Infection Model study scenarios in India: A report

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Introduction

On March 6, 2019, a workshop was held as part of a larger public consultation exercise to evaluate the perceptions of participants from diverse backgrounds of studies involving Controlled Human Infection Models (CHIMs) (1,2) in India, through three specific case scenarios. This workshop was organised by the Health and Humanities Division of the St. John's Research Institute, Bangalore with funding from the Translational Health Science and Technology Institute (TSHTI), Faridabad (www.thsti.res.in), an autonomous institute of the Department of Biotechnology, Government of India This was an on-going effort of the Division to bring public discourse centre stage in the discussion on the use, ethics and regulations related to CHIM studies, and the introduction of such studies in India. Participants included epidemiologists, community/public health experts, microbiologists, infectious disease specialists, basic and translational scientists, ethicists, journalists and lawyers (See names and profiles below*).

The purpose of the workshop was to discuss three CHIM scenarios for diseases of public health importance in India (malaria, typhoid and chikungunya) and understand and deliberate on the relevant scientific, safety, ethical and regulatory considerations Malaria and typhoid infection were chosen as they are important public health problems in India where new vaccines/ treatments may be amenable to testing /using a CHIM model, and for which treatment guidelines are available. While chikungunya infection, also an emerging public health problem in the country, was chosen as a contrasting scenario - viral infection, absence of specific treatment, longer duration, persistent sequelae. The need to explore specific case scenarios evolved from an earlier deliberation during a 14th World Congress of Bioethics Pre-congress Workshop (3) (also organised by the Division of Health and Humanities), where preliminary results of a study on public perceptions to a generic CHIM scenario (3) were presented.

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To cite; Vaz M, Timms O, Rose A, Manesh A, Bhan A. Consultation on the feasibility and ethics of specific, probable Controlled Human Infection Model study scenarios in India: A report. *Indian J Med Ethics*. 2019 Jul-Sep;4(3) NS:239-43. DOI:10.20529/IJME.2019.030

Published online on June 14, 2019.

Process of the Workshop

After an introduction and overview to the workshop, and an explanation of the purpose and process of CHIMs studies, typical typhoid, malaria and chikungunya CHIM scenarios were presented. Participants were divided into three groups with diverse professional representation from the participant pool. Each group had a facilitator and a rapporteur and discussed in detail one of the three CHIMs scenarios using a set of questions which broadly covered the ethical, legal, social, and infrastructural issues specific to the CHIM scenarios.

Plenary presentations by each group generated discussion and raised questions and suggestions for guidance not only pertinent to a specific scenario, but also relevant to CHIM studies in general in India.

It was collectively agreed by the participants that the deliberations of the workshop would be prepared as a report to be published, and used to inform and influence regulations and promote further public deliberation on novel areas in medical research.

Results

Is a CHIM method for understanding responses to a probable Typhoid / Malaria / Chikungunya vaccine relevant for India?

While emphasising that communicable diseases, a significant component of disease burden in India, require novel research and interventions of different kinds, including an overt focus on addressing social determinants of health, the justification for conducting a CHIM study must be very stringent. A CHIM study should only be conducted where really necessary, and, where alternative methods are not useful or have serious limitations and where enough safety measures are in place. "Is there additional information that CHIM studies provide over other methods, such as studying people with the naturally acquired infection and following them up as a cohort population?" "Is there a public health benefit from conducting such studies in India?" were questions frequently raised. The infectious disease researchers emphasised that in many CHIM studies, the disease is arrested prior to the development of complications, often at the stage when infection is detected, even before the development of disease. A concern was raised about the blood draws (the frequency and the amount of blood) from a CHIM participant that were needed to detect onset of the disease while in the research facility, and this was not consistently reported in study documents. It was strongly advocated that disease prevention as a key strategy through improved public health methods and sanitation models should be prioritised alongside any vaccine development; this not being an either-or situation.

Issues raised with respect to specific CHIM scenarios are highlighted below:

Typhoid

CHIM studies have been used elsewhere to evaluate Typhoid vaccines (4).

Typhoid CHIM scenario (hypothetical): Healthy volunteers will be recruited. Well characterised Salmonella typhi strain (Quailes strain) will be administered by the oral route with sodium bicarbonate at a dose of 1-5x104 colony forming units (Dose calculating studies will be needed in the Indian setting). Volunteers will require hospitalization for 28 days (4). Typhoid diagnosis among the study volunteers will be based on symptoms (fever), microbiological blood culture, and Polymerase chain reaction (PCR) tests. Immediate treatment will be initiated for those with clinical symptoms like fever or those who test positive for typhoid even when asymptomatic. Ciprofloxacin, for which the strain used is susceptible, will be the treatment used in the study as it acts against carrier status as well. Participants will be followed-up for carrier status upto a year and will be certified cured before leaving the study facility. Sewage treatment of the facility's effluents will be as per regular hospital rules and infective contaminants will be destroyed.

Group participants raised concerns on the prolonged hospitalisation of typhoid CHIM study volunteers, levels of expected discomfort (given a media report from the UK of a typhoid CHIM volunteer who categorised his participation as 'the worst of my life' (5)), looking into the issue of chronic carrier status, as well as the period of quarantine required, if necessary in a typhoid CHIM study. Questions were also raised if CHIM participation could lead to stigmatisation due to being infected and kept in isolation, and it was suggested that initial CHIM study participants could be involved in community engagement through articulating their experiences of participating in the study. The limited efficacy in real world settings of the existing typhoid vaccines is a cause for concern, and also has implications for herd immunity.

Malaria

CHIM has been used as a model to study malarial pathophysiology, diagnostic tests and vaccines in both high income and low-and-middle income countries. The complexity of the malarial parasite life cycle makes vaccine development difficult. Currently, the only vaccine available for malaria RTSS provides only partial protection against the disease (6) and CHIM studies were used to develop the vaccine (7).

There are two ways of preparing malarial parasites for a CHIM study - rearing parasites, characterising them, and either injecting the cryopreserved P. falciparum sporozoites into the healthy volunteer; or through bites from infected mosquitoes. As explained with the typhoid CHIM model, healthy volunteers would be included in the study. After infection with the malarial parasite, they would be screened twice a day with blood smears and molecular tests for malaria. Volunteers with any symptoms of malaria or positive test will receive prompt anti-malarial treatment (strains used are susceptible to anti-malarials). The volunteers will be hospitalised for the entire study period, (approximately 21 days), and will be declared cured at the end of the hospital stay.

The complications and side effects of Malaria and the treatment drugs were risks that troubled the group. As malaria is one of the oldest, most well-known and well-studied infections, studying the pathophysiology of the disease using a CHIM might not be needed but there is a potential for studying new vaccines using CHIM. Having said that, it was felt that it would be important to understand what can be learnt from earlier malaria CHIMs. Regarding the scientific readiness of India to do a malaria CHIM, the question arose about a relevant, well characterised, stable strain? Would this strain be sensitive to anti-malarial drugs? A pre-condition proposed was the need for the strain to be sensitive to at least three anti-malarials as drug-resistant malaria is a significant global concern. Dosage studies would also be needed, since the dose of the infective agent needed to cause disease could be high in endemic regions.

Chikungunya

Chikungunya is an important cause of acute febrile illness in India and produces chronic morbidity with debilitating joint pains. CHIM studies have not been done with Chikungunya before. Participants felt that CHIM studies on Chikungunya could be complex and difficult. There is also a possible persistence of the virus in joint tissue. Hence, the consensus was that India is far from ready for a Chikungunya CHIM. As and when the science and therapy develop, a Chikungunya vaccine CHIM could be considered for India. Prevention of the disease though effective vector control should be the focus for India in this case. There was little further discussion on a Chikungunya CHIM, but this scenario triggered ethical and regulatory concerns which were relevant to India, particularly about where CHIMs should not be done.

Ethical concerns with CHIM studies

The ethical concerns are summarised below:

- The "intention to harm" by purposefully causing infection in a person makes a CHIM study different from a Phase 1 Clinical Trial which also recruits healthy volunteers. This can be viewed as going against a physician's ethical duty "to do no harm".
- The voluntary, informed and understood consent needed in this situation would have to be reimagined, as it may be unfair and counter-intuitive for a participant to accept harm. 'Two-way consent forms or agreements' were suggested where the researcher/ institution also signs off on long-term obligations to the participant and responsibility of care.
- The money offered for participation appears to be a key motivational factor as per the evidence from other contexts where CHIMs studies have been carried out (5). Is there data on how many times a participant can volunteer

for CHIMs? What is the basis for such a moratorium? There also needs to be a rational balance between compensation and risks.

- Volunteers should be able to reflect and articulate their understanding and motivation to participate. This would help ensure that locally relevant participant safety and protection standards are put in place.
- The issue of the carrier state after the isolation period is important, however low the probability, was discussed. The ethical concern is the implication for extended responsibility of care for the patient and community.

Institutional Ethics Committee (IEC) issues

IECs have a key role in the ethical conduct of clinical trials; reinforced in the recently released New Drugs & Clinical Trials Rules, 2019 (8). There were apprehensions regarding preparedness and capacity of IECs to take responsibility for CHIM studies in India:

- Besides specific training on such studies, IECs evaluating and monitoring CHIMs should involve infectious disease epidemiologists, biologists and public health specialists, as part of its experts' panel. This is especially important as current regulatory requirements for core IEC membership do not usually cover some of these areas of expertise.
- Is there a need for a central designated Ethics Committee for CHIMs at the country level?
- Any SAE in a CHIM emerging from a CHIM study should be evaluated differently from other clinical trials. Hence, specific guidance is needed for IECs monitoring the conduct and SAEs in CHIMs including treatment of possible side effects of therapeutics involved.

Wider social issues

- The media should be engaged early in the process to ensure an understanding of CHIMs studies, and safety measures in place to mitigate harm to the individual and community.
- Inadequacies in the health system and the current climate of mistrust towards clinical research should be kept in mind during the planning stages and management of a CHIM study.
- Questions were raised on the extent of participation of families in the consent stage and in the follow up. Insurance for participants and third parties needed to be explored in this context.

Legal implications of conducting CHIMs

- Caution was expressed regarding the researcher's liability in CHIM studies where participants are purposefully harmed.
- A 'regulatory sandbox' approach was described, where existing legal frameworks can be put on hold and regulations can evolve incrementally by observation of the process in (CHIM) studies conducted at one or two carefully selected institutions with oversight and monitoring.
- There were differences of opinion on whether CHIM studies should be carried out in public or private institutions. The minimum requisites would include track record, accountability, operational, regulatory, ethical and monitoring capacity. An element of public engagement should be in-built.
- If CHIM studies are used to reduce the research time and cost to bring vaccines to the market, the Government should regulate the production of such vaccines and ensure its access by all.

Towards appropriate regulation

Central agencies / individuals commissioned with the task of drawing up guidance for CHIM studies were expected to keep the following recommendations in mind:

- An inclusive process of public engagement as an essential part of developing appropriate regulations, in order to promote transparency and address public concerns
- Groups likely to be directly involved in CHIM studies may be part of deliberations and development of ethical guidelines but this should be viewed with caution, because of possible conflict of interest.
- Only those volunteers who are able to understand CHIM studies and the risks involved, and who can articulate their motivations and concerns about participation should be allowed to be initial participants.
- It was suggested that Central Drugs Standard Control Organization (CDSCO) may not be the appropriate body to regulate CHIM studies. Other government agencies like the Indian Council for Medical Research (ICMR), the Department of Biotechnology, Department of Science and Technology may also be involved in oversight and regulations.
- Approval for CHIM studies should only be given to institutions, whether public or private, which have adequate resources, infrastructure, accreditation and capacity for such research.
- Though CHIM studies would be registered in the CTRI (Clinical Trials registry), a separate national registry may be considered.
- The first CHIM in India should involve a disease that has a proven treatment, public health relevance and a well-characterised local strain.
- Participant feedback through a qualitative interview should be made part of the study protocol and built into the CHIM study implementation design
- Definitions of an SAE in the context of CHIM, reporting protocols, and treatment, should be mentioned in the protocols of the CHIMs.
- A CHIM participant needs to be certified disease-free after at least one year.

Areas of uncertainty

Even after in-depth deliberations, some issues remain unresolved. These include:

1. Decision making – criteria for selecting CHIM as a study design, the organism best suited and regulator
   - In the case of typhoid, for which 2-3 vaccines are already

approved in the market, would an ethics committee consider a CHIM study appropriate for a vaccine new vaccine candidate

- Can a CHIM study replace the evidence obtained from a Phase 3 trial?
- If a private institution provides the inoculum (the well characterised strain), and a successful vaccine is developed, will there be issues of intellectual property or ownership? Is a 'regulatory sandbox' an ethical option?

2. Would insurance companies in India agree to cover CHIM studies as the parameters of risk assessment may be different from drug trials?
   - Would third party insurance be necessary to cover the community in contact with the participant?
   - Would insurance models used in the UK, US and Australia in CHIM studies be applicable in the Indian scenario?

During the workshop, it was revealed that the DBT with the European Union had issued a call for research on a new influenza vaccine initiative which could potentially use a human challenge model (http://www.dbtindia.nic.in/wp-content/uploads/Guidelines-for-Submission-of-Joint-Proposal_NG.-Influenza-Vaccines.pdf). However, it does not specify that the CHIM study needs to be done in India.

Conclusions

Valuable insights and recommendations emerged from the deliberation on the three possible case scenarios of CHIMs in India. The intention was not to approve or disapprove a potential CHIM study, but to use the specific data of the scenarios to explore issues of India's readiness from a regulatory and ethical perspective. It was concluded that:

- A compelling justification for CHIMs is necessary. This includes scientific, legal, ethical and regulatory components. The risks and processes must be supported with robust safeguards.
- The regulatory framework for CHIM studies is complex and different from drug trials.
- Insurance is an important factor to be considered. Long term health insurance coverage for participants may be needed.
- There is need for a multi-disciplinary ethics committee to review CHIM studies with specific domain expertise and training, and for an appropriate Government regulatory body.
- Regulatory and ethical frameworks must be developed in consultation with the public and the various stakeholders; with transparency and due diligence. Desk research along with qualitative data on perceptions of various stakeholders will provide the evidence base for regulations in India.

Participant selection and compensation are important issues for India and that need to emerge from the above process

The deliberations of the experts at the workshop, within the larger schema of public engagement, proved to be a useful exercise. It brought together people committed to the idea of systematic public engagement in research. The public deliberation model provides a forum for ideas to be expressed freely, without reserve, taking on board strong views and dissent, always valuing the intent and context behind the words. The organisers assumed the responsibility of reporting the outcomes of the workshop, collating all views and discussions. The report was shared with the participants, who were given an opportunity to clarify, comment and approve it.

Public engagement in addressing ethical dilemmas and uncertainties of biomedical research is new in India but needs to be an imperative in the development of relevant regulations (9). It is an evolving process, not limited to a single meeting, but a series of deliberations and negotiations.

***Disclosure**: While these deliberations have been conducted with funding as a grant from THSTI, Delhi, the recipients of the grant had complete independence to analyse the data and publish the report, independently of THSTI.*

Acknowledgements: The participants of this meeting are acknowledged for their time, insights and feedback. : Abi Manesh, Department of Infectious Diseases, Christian Medical College , Vellore; Amrita Sekhar, Consultant, Translational Health Science and Technology Institute, N Delhi; Anant Bhan, Researcher, Bioethics & Global Health, Saket Nagar, Bhopal; Anuradha Rose, Dept of Community Health, Dept of Bioethics, Christian Medical College, Vellore; Avita Johnson, Dept. of Community Health, St John's Medical College, Bangalore; Chandra Mouli Natchu, Division of Infectious Diseases, St John's Research Institute Bangalore; Denis Xavier, Division of Clinical Research and Training, SJRI, Dept of Pharmacology, St John's Medical College, Bangalore; GD Ravindran, Dept of Medicine, Medical ethics, St. John's Medical College Bangalore; Jayanthi Savio, Dept. of Microbiology, Member Secretary, Institutional Ethics Committee, St John's Medical College Bangalore; Kalpana Subramanya, lay member, St John's Medical College IEC Bangalore; Mala Ramanathan, AMCHSS, SCTIMST Medical College, Trivandrum; Manjulika Vaz, Health and Humanities Division, St John's Research Institute Bangalore; Mario Vaz, Health and Humanities Division, SJRI, Dept of Physiology, St John's Medical College Bangalore; Mary Dias, Division of Infectious Diseases, SJRI, Prof Dept of Microbiology, St John's Medical College Bangalore; Nikita Surani, Forum for Medical Ethics Society, Pune; Olinda Timms, Health and Humanities, SJRI, Bangalore; Radhika Hegde, History of Medicine, SJMC Bangalore; Rahul Matthan, Advocate, Trilegal Bangalore; Rakhi Ghoshal, Indian Journal of Medical Ethics, Mumbai; Rashmi Rodrigues, Dept of Community Health, St John's Medical College Bangalore; Rathna Kumari, Social Scientist, Community Health Dept, St John's Medical College Bangalore; Ravi Vaswani, Dept of Medicine, Yennepoya University, Mangalore; Sandhya Srinivasan, Independent Journalist and Researcher, and Consulting Editor, Indian Journal of Medical Ethics, Mumbai; Savitha Sebastian, Dept of Medicine, St John's Medical College Hospital Bangalore; Sudhir Krishna, National Centre for Biological Sciences, Tata Institute of Fundamental Research, Bangalore; Suraj Jagtap, Division of Biological Sciences, Indian Institute of Sciences Bangalore; Uma Kulkarni, Dept of Ophthalmology, Centre For Ethics, Member Secretary, Yenepoya*

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Teaching bioethics to postgraduate students in a public sector university: A report from Karachi, Pakistan

NAZLI HOSSAIN

Bioethics is not taught as a subject discipline in the undergraduate and postgraduate curriculum in Pakistan. Recently, medical colleges have introduced the behavioural sciences in the undergraduate curriculum, but this has its own limitations, as students are not examined at the end of course work, as in other subjects, which they have to clear in order to get promoted.

The regulatory body of the country, the Pakistan Medical and Dental Council, revised the curriculum in 2014, introducing Medical Ethics (1). The discipline is limited to a few hours of tutorials, and hence not given due weightage in the final examinations. The topics identified under the heading of Medical Ethics include the National Recommended Guidelines, the Code of Medical Ethics and background concepts and components. These components are taught for the first four years of medical studies, with a total of 14 lectures. There is no formal assessment, as for other subjects. for this subject. As a result, students miss the tutorials, as they know in advance that they will not be examined on this knowledge. This is the only formal education which the undergraduate may attain in biomedical ethics at undergraduate level, in all medical colleges in the country. Whatever they learn later is from their own experience, by observing their peers, mentors and supervisors. The same holds true for postgraduate students. They are not taught biomedical ethics at all, and their supervisors become their "books" in the discipline of bioethics.

I have worked as an obstetrician and gynaecologist at a public sector hospital, for the last 25 years. My college and hospital is located in the vicinity of the. Center of Biomedical Ethics and Culture (CBEC), of the Sindh Institute of Urology and Transplantation (SIUT). This is the only institute in the country imparting formal degree level education in the discipline of Biomedical Ethics. Both the medical college and the hospital

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To cite: Hossain N. Teaching bioethics to post graduate students in a public sector university: A report from Karachi. *Indian J Med Ethics.* 2019 Jul-Sep;4(3) NS:243-5. DOI:10.20529/IJME.2019.034

Published online on July 3, 2019.