A REPORT OF THE CONSULTATION ON THE FEASIBILITY AND ETHICAL ISSUES IN SPECIFIC, PROBABLE CONTROLLED HUMAN INFECTION MODEL (CHIM) STUDY SCENARIOS IN INDIA

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INTRODUCTION

On 6th March 2019, a workshop was held as part of a larger public consultation exercise to evaluate the perceptions of participants from diverse backgrounds to 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](http://www.thsti.res.in)), an autonomous institute of the Department of Biotechnology, Government of India . The workshop was part of an on-going effort of the Division to bring public discourse at the 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. Many of the participants had multiple roles. (See table 1)

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 the relevant scientific, safety, ethical and regulatory considerations. 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.

Box 1: The reasons for the selection of the three CHIM scenarios

Of the three case scenarios presented at this workshop, 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. The third scenario – 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) to enable deliberation on issues where CHIM should not be implemented and clarify where the lines for CHIM studies might need to be drawn.

PROCESS OF THE WORKSHOP

After an introduction and overview to the workshop, infectious disease specialists who were part of the organizing group presented a brief overview of the purpose and process of CHIMs studies followed by factual scenarios for Typhoid, Malaria and Chikungunya CHIMs. 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 (See Appendix) 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 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.

TABLE 1: Profile of Participants

|  |  |
| --- | --- |
| **Domain** | **No of participants** |
| Basic Science (Microbiology, Immunology, Molecular medicine, | 8 |
| Social Sciences | 4 |
| Public Health / Community Medicine | 5 |
| Clinical medicine/ infectious diseases specialist | 4 |
| Ethics – Ethicists, Trainers, Researchers, IEC members | 11\*\* |
| Lawyers | 2 |
| Communication and Media specialists | 2 |

\*\* fell into more than one domain

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 cause 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 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: Typhoid remains an important clinical problem in the Indian setting and there is a need for more effective Typhoid vaccines. CHIM studies have been used elsewhere to evaluate Typhoid vaccines. There are no animal models for typhoid. A brief outline of a possible typhoid CHIM scenario is outlined below.

*Typhoid CHIM*: 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 14 days. Typhoid diagnosis among the study volunteers will be based on symptoms (fever), microbiological blood culture, and biomarkers. 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.

Bharat Biotech has produced a conjugate Typhoid vaccine, which was also tested in a CHIM study at the University of Oxford.

Group participants raised concerns around the need for the prolonged hospitalization of typhoid CHIM study volunteers, level of expected discomfort (given a media report from the UK of a typhoid CHIM volunteer who categorized his participation as ‘the worst of my life’ (4)), looking into the issue of chronic carrier status, as well as the period of quarantine required, if necessary in a typhoid CHIM study. It was also necessary to explore if CHIM participation could lead to stigmatization of any kind for participants, and if 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: Malaria remains a common clinical problem in India contributing to significant morbidity and mortality. 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 RTS,S provides only partial protection against the disease (5) and CHIM studies were used to develop the vaccine (6).

There are two ways of preparing malarial parasites for a CHIM study - rearing parasites, characterizing 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 and will be declared cured at the end of the hospital stay.

The complications and side effects of Malaria in those with compromised immunity were risks that troubled the group. As malaria is one of the oldest and 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. No specific antivirals are available for this infection and treatment is mainly symptomatic. 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 regard to CHIM studies**

The ethical concerns, at the philosophical and applied levels with regards to CHIM studies in general were extensively discussed, and are summarized below:

* There is an “intention to harm” in a CHIM study by purposefully causing infection in a person, which makes a CHIM study different from a Phase 1 Clinical Trial where similarly a healthy volunteer is recruited. Purposeful infection of participants can be viewed as contradictory to a physician’s ethical duty to do no harm.
* If voluntary, informed and understood consent is a way to address this concern, then consent forms in the present form could be considered unfair and onerous, as they put an unusual burden on the participant of acceptance of harm. It was suggested to have ‘two-way consent forms or agreements’ where the researcher/ institution signs off on long-term obligations to the participant and responsibility of care.
* What are the drivers for participation in CHIM studies? The money offered for participation appears to be a key factor as per the evidence from other contexts where CHIMs studies have been carried out. There have been situations in the UK and Kenya of people participating in multiple CHIMs. Is there data about how many times a participant can volunteer for CHIMs? What is the basis for this moratorium? There 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. The ethical concern is the implication for extended responsibility of care if the person remains a chronic carrier, with the risk of spreading infection.

Institutional Ethics Committee (IEC) issues

In the present clinical trial review and monitoring process in India, IECs have a key responsibility for ethical conduct of clinical trials, participant protection, establishing causality for serious adverse events (SAEs), and compensation for SAEs, including death. These have been reinforced in the recently released New Drugs & Clinical Trials Rules, 2019 (7). During the workshop, there were repeated apprehensions expressed regarding IECs and their ability to take responsibility for CHIM studies if they had to begin in India:

* Expertise of IECs and need for training on the special ethical issues for CHIM studies emerged as being very important. IECs evaluating and monitoring CHIMs should involve infectious disease epidemiologists, biologists, public health specialists, clinicians, health systems experts as part of its membership/external experts’ panel. This is especially important as current regulatory requirements for core IEC membership do not usually cover some of these areas of expertise.
* Cost justification for CHIMs needs to be factored in. Are IECs equipped to debate these issues?
* It would be perhaps necessary to have specially trained Ethics Committees for CHIMs, particularly for the first few studies being conducted in the country.
* How is an SAE determined in a CHIM? Any complication in a CHIM should be an adverse effect. But there is need to differentiate between symptoms of infection and complications of the infection. Hence, specific guidance is needed for IECs monitoring the conduct and SAEs in CHIMs.

**Are there wider social issues that should be kept in mind?**

* There were social issues related to the media and the community. Perceived risks of infection spread to the community could be conveyed by the media which need not even be true, but which could result in stigmatisation of CHIMs participants. Hence, the media should be engaged early in the process rather than later to ensure they understand the role of CHIMs studies, and how these are conducted.
* The current climate of mistrust towards clinical research could be construed as being non-conducive to starting CHIM studies in India. As the duration of follow-up is very important for a CHIM trial, accountability and quality of the health system is critical. Deficiencies that exist in this area in India need to be addressed. A reliable health system will allow for easier conduct of vaccine trials.
* Should the families of participants in CHIM also be consulted and looked after? It was argued that inclusion of the family of the participant was important in the consent process. Insurance needs to cover third parties affected / infected as well.

**Legal ramifications of conducting CHIMs**

* A physician’s duty to care and not harm, may put the physician-researcher in a legally vulnerable situation.
* There was a suggestion from a legal expert, of a ‘regulatory sandbox’ approach where existing legal frameworks can be put on hold and regulations can evolve and be enhanced incrementally by observation of the process in (CHIM) studies conducted at one or two carefully selected institutions permitted to do CHIMs with careful oversight and monitoring. Learning from this experience can then be used to inform oversight norms and regulations.
* Research institutions would need to be chosen with extreme care, since concerns and challenges could significantly differ between private, public and public-private partnerships. The minimum requisites would include track record, accountability, operational, regulatory, ethical and monitoring capacity and a commitment to long term follow up and care of the participant. An element of public engagement should be in-built.

**Towards Appropriate Regulations**

Box 2: Some background information on the existing regulations that may apply to CHIM studies. (These were not presented or discussed at the meeting but are provided for contextual understanding)

At present, in India, research using hazardous microorganisms, genetically engineered (GE) organisms & products thereof are governed under Rules, 1989 (Rules for the Manufacture, Use/Import/Export and Storage of Hazardous Micro Organisms/ Genetically Engineered Organisms or Cells) of Environment (Protection) Act, 1986, according to which, necessary intimation/ recommendation/ authorization from concerned Institutional Biosafety Committee (IBSC), Review Committee on Genetic Manipulation (RCGM) & Genetic Engineering Appraisal Committee (GEAC) is obligatory based on type & scale of research operations. Further guidance on regulatory considerations can be obtained from: Guidelines and Handbook for IBSCs, 2011 (<http://www.dbtindia.nic.in/wp-content/uploads/9.-Guidelines-_Handbook_2011.pdf>) , Regulations and Guidelines on Biosafety of Recombinant DNA Research & Biocontainment, 2017 (<http://www.dbtindia.nic.in/wp-content/uploads/Draft-Biosafety-Regulations-andBiocontainment-Guidelines-2017-FF.pdf>) and Recommendations for Streamlining the Current Regulatory Framework, 2005 (<http://www.moef.nic.in/divisions/csurv/geac/draftreport_rpharma.pdf>)

The participants had strong views on the need to influence the development of appropriate regulations for CHIMs in India. The organisers reiterated that the inclusive process of public engagement was specifically targeted at this objective. Central agencies / individuals commissioned with the task of drawing up potential guidance for CHIM studies need to be enjoined to include these considerations and recommendations as well as committed to the need for transparency.

* Participants from sub-sections of the public likely to be involved in/who understand CHIM studies should be part of the deliberations towards developing ethical frameworks. On the other hand, those who are likely to conduct CHIM studies should be involved in the deliberations, but their participation in the development of the overarching ethical frameworks and regulatory guidance should be viewed with caution, because of the possibility of conflicts of interest.
* Participants in the initial CHIM studies should be individuals who are able to articulate their experience, concerns, reasons for participation, and understanding of CHIM studies.
* It was deemed inappropriate for the Central Drugs Standard Control Organization (CDSCO) to be vested with the sole duty to regulate CHIM studies. Other relevant government agencies like the Indian Council for Medical Research (ICMR), the Department of Biotechnology, Department of Science and Technology being also involved in oversight, or setting up a special multi-agency committee were options that were mooted for providing leadership and overall supervision for CHIM studies, working with the CDSCO.
* Regarding appropriate institution (s) suited for the conduct of CHIMs, a thorough checklist of mandatory resources and infrastructure had to be developed. Reasons for this were the current scenario of inadequate trust in the quality of healthcare service and healthcare research institutions in India. Certain private institutions could have more credibility than public ones; though public ones are inherently expected to be more trustworthy and accountable.
* Ensure a national registry for CHIMs in India which would be separate from the Clinical Trials registry, though CHIM studies would also be registered in the CTRI. This could contribute towards facilitating a global sharing of CHIM findings. A global registry which allowed for tracking CHIM studies in other settings was also necessary, as it would allow for investigators and other stakeholders to be aware of other ongoing CHIM studies, and study outcomes.
* 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 Contention / Uncertainty**

The in-depth discussions and information-sharing threw up contentious issues that lacked convincing answers or assurances. These remain grey areas that require further deliberation and comment by the regulatory authority.

* Decision making – who decides whether a particular CHIM study should be done or not?
* 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 vaccine new vaccine candidate? Since the other vaccines were evaluated differently?
* What is the extent of data that a CHIM study can reveal? Would a Phase 3 trial still be needed?
* Should the CHIM microorganism be classified as a ‘biological’ agent or ‘organism’? This needs clarification, as it affects the regulatory jurisdiction of these studies.
* If a private institution is involved in providing the inoculum (the well characterised strain), and a successful vaccine is developed, will there be issues of intellectual property or ownership? Also, shouldn’t the State take on the responsibility of building or reviving its vaccine manufacturing units (including GMP facilities)
* Which regulatory body should govern CHIMs in India? Who will develop the regulations for conducting CHIMs?
* How ethical would a ‘regulatory sandbox’ be?
* Would Insurance companies in India agree to cover CHIM studies? It was argued that insurance is essentially risk-assessment analysis. Will the algorithms for other research studies also apply for CHIMs?
* How will third party insurance be formulated as the entire population is exposed to the natural infection to some degree? Should the larger community be protected?
* Would insurance models in the UK, US and Australia dealing with CHIMs be worth understanding to start the negotiations with Indian insurance companies?

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 (<http://www.dbtindia.nic.in/wp-content/uploads/Guidelines-for-Submission-of-Joint-Proposal_NG.-Influenza-Vaccines.pdf>), and that the call asked for the validation of the vaccine candidate in a human challenge model of influenza. However, it does not specify that the CHIM study needs to be done in India. This was not clear to the participants and organisers at the time of the workshop.

CONCLUSIONS

Varied and 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 very important. This includes scientific, legal, ethical and regulatory components. The risks and processes must be supported with robust remedies.

• The legal basis for CHIM studies appears complex and different compared to drug trials.

• Insurance is an important factor to be considered. Long term health insurance coverage for participants needs to be assured.

• There is need for a multi-disciplinary ethics committee to review CHIM studies with specific domain expertise (including public health/epidemiology) and special training, and for an appropriate Government body/multi-agency committee to regulate these studies

• Overarching regulatory and ethical frameworks must be developed in consultation with the public 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 needs to emerge from the above process
* Specific engagement is required with the scientific and regulatory community, prospective participants, the media and the public.

Finally, the deliberations of the workshop within the larger schema of public engagement proved to be a useful exercise and a process of relevance for ethical research in India; possibly in other LMICs too. It brought together people who have many decades of public engagement in the fields of social development, community health, epidemiological research, and health policy; all committed to the idea of systematic public engagement. In a public deliberation, there must be room for people to express their ideas freely and without reserve. People may express strong views and even dissent – their words matter but the intent and context behind the words are equally important. During the deliberation, ideas evolve, people’s views change, sometimes converging, sometimes diverging. The organisers assume the lead in reporting the outcomes of the workshop with great responsibility, collating all views and discussions. Reporting of individual views has been avoided and a collaborative, inclusive process has been followed, despite the effort this entails. 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(8). It is an evolving process, not limited to a single meeting, but truly engaging with all stakeholders and the public through a series of deliberations and negotiations with investment of time and resources.

We hope that the organizing of the workshop and sharing of the key discussions will pave the path to further efforts towards public engagement in science and medicine in India.

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Appendix

QUESTIONS FOR DELIBERATION IN SMALL GROUPS

1. Is the information in the scenario provided to you sufficient to explain the relevance in India for a CHIM study with this infection? Can you attempt to identify and address the gaps?
2. In your group’s view, is it feasible to conduct such a CHIM in India within a reasonable timeframe? Provide your recommendations with regard to the challenges.
3. Have the ethical safeguards been addressed? What would require further strengthening (Ethical, legal, social, regulatory issues) and why? Can you prioritize your recommendations?