Title: Conducting Controlled Human Infectious Model (CHIM) studies in India is an ethical obligation.

Abstract:

Actual obligations and prima facie obligations conform closely to human experience as moral agents and provide indispensable categories for biomedical ethics. Weighing competing prima facie obligations and achieving the “greatest balance” of right over wrong helps determine actual obligations and guides an individual, an agency or a country to determine what ought to be done in a challenging situation. Conducting controlled Human Infection model (CHIM) studies in India is one such situation.

The ethical challenge in conducting a CHIM study lies in achieving the difficult task of balancing the push of scientific merit in introducing standardized, attenuated strains of micro-organisms into normal healthy volunteers to develop knowledge which adds value to the society with the pull of ensuring safety of these healthy individuals to potential and completely informed risks in a fashion that is transparent, accountable and open to public view. The bar is further raised in the background of already fragile public confidence in biomedical research in India; especially when “deliberate” introduction of microbial agents to healthy individuals is involved for the larger altruistic gain intended to help the society as a whole.

This paper introduces what a CHIM study is and goes on to discuss the uses of CHIM studies with respect to the larger scientific Indian research fabric of the 21st century. It further explores etic and emic perspectives in conducting such trials in India and generates an ethical coherence in an attempt to justify conducting CHIM studies in India. The paper deliberates on ethical issues arising out of conducting CHIM studies and provides obligatory reflections on how developing capacity for CHIM studies in India is likely to strengthen the health research and development sector in the country.

Introduction:

The strength of any country’s ethical research fabric lies in how and in what way the scientific discourse benefits both--the country’s public health and the scientific industry. Clinical Trial operations in India are not in alignment with her health care needs and have skewed away from Infectious diseases like Tuberculosis, Malaria with an unfairly large proportion of registered trials focusing on non-communicable diseases like Cancer and Diabetes(1). This is despite the fact that the global burden of disease survey for 2016 showed that communicable, maternal, neonatal and nutritional diseases (CMNND’s) contribute to 24.8% of the overall disease burden in India(2),(3). Infectious diseases in India have the highest Disability Adjusted Life Years (DALYs) but account for only 5% of the total clinical trials registered between July 2007 and December 2015. Interestingly, a large proportion (46.6%) of these trials were phase III trials and only 6.5% were phase I trials(4).

This skew towards phase III trials understandably prevents scientific and technological enhancement of the Indian scientific community; phase III trials are, after all, trials which test already tested drugs on a larger patient population whereas phase I trials involve health human volunteers and hence require much more scientific expertise and ethical and regulatory preparedness(5). Safety of the participants who take part in these “first in man” studies is a combined social, moral and scientific responsibility of the research community.

Is the Indian scientific-ethical research fabric strong enough to bear the responsibility of such trials? As of now, legal and regulatory requirements allow trials involving healthy human volunteers only for indigenously developed drugs and patents or foreign drugs which are already tested or are being concomitantly tested in healthy human volunteers elsewhere(6).

In this background, this essay argues the scientific and ethical merits of a specific trial design which involves introduction of specially developed attenuated strain of microorganism into health human volunteers.

In order to understand the study design completely, the paper presents the definition and overview of a CHIM study design, discusses the uses of CHIM studies and debates about shifting the question from whether CHIM studies are ethically permitted or not to CHIM studies being ethically required in India.

The paper goes on to present the inside(emic) and the outside(etic) perspectives to CHIM studies in India and attempts to integrate both views to justify conducting CHIM studies in India as a moral obligation, an ethical duty which is likely to benefit the public at large and the scientific community as a whole.

**Defining a CHIM trial: What and How of a CHIM study design**

This section summarizes some of the scientific, technical and community related issues involved in a CHIM study.

A typical Controlled Human Infection model is a Phase I trial involving intentional introduction of a pathogen of public health importance, a pathogen whose pathogenesis is well understood, and which is administered through a known and standard route in a specific dose, and which does not cause any persistent infection or post-infection sequalae. Table 1 summarizes the characteristics of an Ideal pathogen strain for a CHIM study(7),(8),(9),(10),(11).

Table 1: A typical Controlled Human Infection Model-Pathogen strain characteristics.

|  |  |
| --- | --- |
| An ideal pathogen strain characteristics for CHIM study. | Example of various pathogen strains used in CHIM studies. |
| 1. Needs to be of public health importance. | *P. Falciparum 3D7, NF54, and 7G8 strains, S. Typhi (quales strain), Noro virus strain G2.1, G2.2, G2.4, H.Pylori strain BCS100, Vibrio Cholera 01, Tor Inaba strain N16961, E.Coli expressed recombinant SERA-5(Honduras-1) for Malaria.* |
| 1. Pathogenesis of the strain is well understood, including incubation periods, course of the illness etc. |
| 1. Does not have or has an ineffective animal model. |
| 1. Does not have persistent infection or post-infection sequalae. The illness caused by the organism has to be either self limiting, reversible or have a standard effective treatment option. |
| 1. Has well defined definition of “infection” and “disease” and possibly has defined biomarkers for both. |
| 1. Has a standardized methodology of Inoculum preparation, are mostly attenuated strains prepared under Good Manufacturing Practice (GMP) guidelines and preservation which can be reproduced and disseminated. |
| 1. Have a standard dose and a standard mode of administration and standard mode of assessment (screening test) of infection/disease. |
| 1. Has predictable and measurable immune response and has well-defined immune, clinical and non-clinical end points which can be measured separately in the laboratory. |
| 1. Has known vectors which can be bred in controlled environments. |

***Selection of subjects:***

The well-standardized strain of pathogen in a CHIM study is then introduced into carefully selected participant healthy volunteers. These volunteers typically go through several stages of screening and are typically well-educated, well-nourished, young, healthy individuals with normal immune systems. The recruitment process should be able to answer the questions mentioned in table 2(12),(13),(14),(15).

Table 2: Volunteer screening and selection in a typical CHIM study design:

|  |  |
| --- | --- |
| Questions: | Points of reflection relevant to Indian setting: |
| 1. Is there fair selection of subjects? | * Social vulnerability in terms of poverty driving participation; * competence vulnerability in terms of ability to understand and * Inherent vulnerabilities of language, cultural differences and * Issues of family/individual consent. |
| 1. Has the risk-benefit ratio been explained to and understood by the proposed volunteers? Is there a personalized risk-benefit statement been made by the participant? | * Open discussion on risks, discomfort, lack of direct benefit, purpose of enrollment, procedures involved including isolation (if involved), * concept of individual risk vs. tangible social benefit from the trial, and * Degree of compensation for risk vs. harm involved in participation. |
| 1. Have efforts been made for community participation and engagement? | * Community sensitization through focused group discussion platforms to build transparency and accountability. |
| 1. Has the participant undergone a fair informed consent process? | * Adequate process for clarifications, freedom for refusal to participate, confidentiality of information shared. |

***Safety considerations of participants:***

Safety of the participant in a CHIM study is paramount and starts from the point of choosing the type of pathogenic strain used to having a rigid inclusion and exclusion criteria about volunteer participation and vigorous screening measures for medical and psychological vulnerabilities. This can include a detailed vaccination history, review of past medical records and psychological assessments as per need. Table 3 summarizes the various factors that need to be considered in order to ensure safety of the participants in a CHIM study(8), (16), (17),(18),(19).

Table 3: Factors that need to be considered in order to ensure participant safety in a CHIM study:

|  |  |
| --- | --- |
| Factors | Salient points |
| 1. Microbiological factors | * Choice of a strain with easily identifiable symptom profile and availability of prompt treatment, * Separate and detectable microbial and clinical endpoints which can be easily monitored. * Clear methods to confirm infection clearance or resolution. |
| 1. Pathogen specific factors | * Using attenuated pathogen strains. * Using strains which are antibiotic sensitive and testing antibiotic sensitivity before the trial. |
| 1. Setting specific factors | * Academic or commercial facilities which foster trust and have state of art diagnostic investigation, transport and treatment pathways. * An adequate facility for isolation (if required) which provides adequate physical and psychological well-being environment for participants and allows prevention of spread of infection in the general community. |
| 1. Participant specific factors | * Selected volunteers carefully screened for social, competence and individual vulnerabilities. * Well-informed participants who are at minimal risk of having incidental illnesses. * If participant is from an endemic setting, consideration of environmental hygiene and sanitation infrastructure, vector circulation needs to be considered to ensure community safety. |
| 1. Regulatory factors | * A detailed independent review and oversight by a competent regulatory body which ensures monitoring of the trial at all stages |

**Why use Challenge studies? Scientific merit of Controlled Human Infection models.**

Well-regulated Challenge studies following universal scientific and ethical standards as described above have been a part of scientific discourse of many countries for around 70 years now. More than 20,000 volunteers have taken part in around 143 trials in developed countries and 12 in low and middle income countries till date and have contributed to answering important scientific and public health enquires as mentioned below:

1. To understand and evaluate transmission of infection:

CHIM study protocols have been developed to understand the transmission cycles of various pathogens inside the human body. A recent example is of a controlled Human Malaria infection model which studied gametocyte transmission of P falciparum from humans to mosquitoes; this can have future implications in developing transmission blocking interventions to prevent spread of malaria(20).

1. To understand pathogenesis or human immune response to various pathogens.

This is by far the most common use of challenge models. This is especially valuable for pathogens for which no suitable animal model exists. A good example would be the BCG human challenge model which provided important data on anti-mycobacterial immunity because of poorly understood animal data on immune responses to the same(21).

1. Use of CHIMs in Vaccine studies.

There has been growing interest in using challenge strains of micro-organisms to study vaccine efficacy by administrating these strains at some point in time after vaccination. These are essentially proof of concept trials which eventually help to fast-track vaccine development by checking its efficacy on smaller number of human volunteers and prevent unnecessary exposure of thousands of people in larger Phase III trials. One good example of the same is how an Indian Vi-tetanus toxoid conjugate vaccine developed by Bharat Biotech showed 87% efficacy in protection against typhoid fever in a phase IIb randomized control study using a human challenge model by an Oxford Vaccine group in the United Kingdom(22),(23).

1. Use in Vaccine screening.

Challenge models are used to assess potential vaccine candidates before subsequent development stages of the vaccine. This essentially means helping researchers to up-select or down-select potential vaccine candidates and thereby avoids large scale, expensive field testing of these vaccines. Example of this include use of radiation attenuated a malaria vaccine using plasmodium sporozoites which can induce sterilizing immunity against challenge models of infectious sporozoites in human volunteers(24).

1. Use as therapeutic interventions.

Challenge models are used as direct therapeutic approach or aim to test the efficacy of a therapy after direct infection by a challenge strain. Examples of this include investigational therapeutics to treat Shigellosis in various *shigella Flexneri* models(25).

1. Use in Dose Escalation studies

Another area where challenge models are used is to determine challenge dosages needed to reach specific attack rates—example of this include salmonella Typhi dose escalation studies in an ambulant model design to advance understanding of host-pathogen interactions and immunity at different doses of exposure to Salmonella Typhi(26).

1. For studying various facets of infection and derived immunity in humans.

Human Challenge studies are the most obvious way to prove causality. Unlike past self-challenge serendipitous discoveries, well regulated CHIM studies have been able to identify rhinovirus as the main cause behind common cold. Another important area where CHIM studies have contributed is in knowing important virulence factors and identifying mechanisms underlying host susceptibility. An example of this is the N. Gonorrhoae IgA1 protease deficient strain challenge model which attempts to assess its potential virulence in male volunteers(27).

**Does India need CHIM studies? Emic and Etic perspectives to the *Idea* of conducting CHIM studies in India:**

As is evident, CHIM studies are technically challenging and ethically demanding as it attempts to balance the acceptable levels of risk to healthy human volunteers with a transparent and truly informed Informed Consent process. CHIM studies are also socially compelling as though they do tend to answer questions of public health importance; they also demand community participation and sensitization to the nubilous concept of risk-benefit ratios in research.

So, does India need these types of ambitious projects at all? Can’t we do without them? Are CHIM studies a ‘want’ or a ‘need’ for the Indian society? What is the social value of such studies in India?

An ethical enquiry into the need of CHIM studies for India would require one to use both emic and etic perspectives to understand the relevance of such studies in the Indian cultural fabric. The subsequent sub-section weighs conflicting prima facie obligations using the reflective equilibrium approach(28) to reach a state of balance justifying conducting CHIM studies as a moral obligation.

**An Emic (from Inside) perspective**:

CHIM studies, from an emic perspective of an average healthy participant volunteer, would raise incoherence in the Indian ethical-research fabric which needs to be adjusted and pruned to reach a reasonable reflective equilibrium.

First and foremost, these studies challenge the considered judgment of *primum non nocere—“*Above all, do no harm” and floods the average, informed Indian healthy volunteer with the appalling historical memories of unregulated science experiments done by the Nazis and the Tuskegee experiments on normal human volunteers which would be clearly considered unethical in this age(29),(30). The Indian research fabric has seen turbulent times with reports of direct harm to uninformed vulnerable participants in the now infamous Phase III trials conducted in Indore and Bhopal (2004) and Human Papilloma virus vaccine trials involving tribal girls in Gujarat and Andhra Pradesh (2010)(31),(32),(33),(34).

However, the argument which prunes the considered judgment is that the starting point of a CHIM trial is a well-informed, healthy, adult volunteer who has clearly understood the risks involved in participation and is carefully selected through a transparent and accountable informed consent process and not an individual vulnerable on account of social, individual or competence vulnerabilities. A robust informed consent process is an absolute necessary but may not be sufficient pre-requisite for any phase I trial. The participant in a CHIM trial is also someone who has understood known, unknown and potential risks involved and again, the engaging point is not an ill-defined or a general risk expression; it is a clear, unambiguous communication of defined risk with respect to the concerned CHIM model. And as Evans and Evans have put it—“when research is avowedly non-therapeutic, we could say that the risks are minimal if the research procedure involves no foreseeable harms which are either more likely or more severe, than those that one could meet in everyday life. It is expected that daily life, involves a certain amount of risk, after all”(29).

Taking the pruning process further, “a well informed healthy volunteer completely aware of the risk involved and such CHIM studies are good for India” might be a necessary pre-requisite but may not be sufficient to justify a CHIM trial in India where the social value of any research is seen at par if not above the scientific rigor of the research design. Most of the diseases that challenge models investigate for pathogenesis, immunity, treatment or vaccines studies are endemic in India. From an emic perspective, CHIM studies in disease endemic settings provide better understanding of genetics, pre-exposure, immune status and environmental factors that play a role in disease manifestation. The potential social benefits of generating evidence from a country’s own population and for the benefit of their own society make ethical, social and political sense. Alternatively, arguing against using evidence generated from a socio-ethnographic different population for Indian population (e.g. Efficacy of Indian Typhoid vaccine tested in Oxford) makes the moral judgment bend towards conducting CHIM studies more coherent and inclusive.

**An Etic (from outside) Perspective:**

From an etic perspective, an important considered judgment to begin with would be that involving distributive justice—with dramatic inequalities in access and exuberant increase in costs of health care, would it be fair and equitable for the scientific Diaspora to invest limited resources in demanding trials like a CHIM in a resource poor country like India?

In order to answer this complex question—let’s look at the concept of what constitutes a fundamental need. If the essential social resource, including a subset of health care, if not distributed according to need, the individual/community will suffer a harm or at least a detrimentally affect—this defines a fundamental need. Though the need for CHIM studies from science side is clear, as seen from an etic view, becomes an ethical obligation only when it resonates with the concept of a fundamental need. A Controlled human infection model hypothetically would allow assessment of a preliminary vaccine or assessment of human immune response to a particular pathogen. Suppose this shows that a candidate vaccine to be ineffective; this would prevent unnecessary exposure of thousands of people to large and costly Phase III trials. Though the human challenge trials may not be an alternative to phase III trials, they would help in licensing a product followed by strict post marketing surveillance as is evident from development of Cholera vaccine Dukoral and typhoid vaccine Ty21a. Also, not using a CHIM design and exposing general population to vaccine candidates tested for efficacy in animal models could amount to harm or at least a detrimental effect knowing that animal models are often inadequate predictors of immune response.

Having seen as a fundamental need, provision of other fundamental needs like basic sanitation and hygiene services for prevention of communicable diseases stands alongside and not as either/or to provision of opportunity to take part in a CHIM trial and justifies this scientific advancement for public benefit from an etic perspective.

**Towards an integrated approach: Justifying the *Act* of conducting a CHIM study in India.**

Thus, with consistency and coherence using argumentative support and restriction of starting premises to considered judgments, both emic and etic perspectives seem to justify the *Idea* of a CHIM study for Indian population.

Justifying the *Act* of actually conducting a CHIM study in India would require procedural justice to be implemented at all steps of a CHIM study. Developing adequate infrastructure and clinical services which allow volunteer participants to be engaged outside their home environment for a stipulated time period, developing laboratory facilities and infrastructure requirements for developing and regulating delivery pathways to locally relevant strains of pathogens under Good Manufacturing Practices (GMP) guidelines seems to be the first procedural step towards conducting CHIM studies in India.

The second and equally important step would be to develop scientific rigor to structure protocols for fair selection of participants and ensure a robust Informed consent process.

Community participation, transparent public engagement, assessment of motivation for participation and justified provision of compensation for the risk/harm for the participant provides a trust building third step.

Fourth and finally, ensuring and implementing regulatory policies for safety of the volunteers participating in CHIM studies in India can be achieved through a robust regulatory environment supported by law which meets and enforces high regulatory standards of care provided to the participants.

**Challenges and Recommendations:**

Obligations and rights always constrain individuals unless a competing moral obligation or right can be shown to be overriding in a particular circumstance. As Ross puts it, “the greatest balance” of right over wrong must be found(28). This bioethical enquiry into the need of Controlled Human infectious model or CHIM studies through emic and etic perspectives using reflective equilibrium does justify conducting CHIM studies in India as a moral obligation.

Notwithstanding the compelling scientific and ethical merits of the argument, moral residue of driving people to collaborate and convince people to act according to local needs, providing a transparent and strong regulatory platform to conduct CHIMs where all stake-holders are harmonized with trust as a central ingredient into a common agenda to ensure safety of the participants remains the major challenge before closure of this ethical discourse(35).

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