Public Engagement in the context of a CHIM study

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New or mutated pathogens or more virulent strains causing disease outbreaks have emerged with rapidly changing circumstances and have taken the medical community by surprise. The E-bola and Zika virus outbreaks in the recent past are cases in point. The exact mechanism of infectivity in humans and their pathogenesis needs to be determined if such diseases are to be controlled, whether by preventive measures or appropriate treatment.

India has clear ethical guidelines and regulations for the conduct of clinical trials of drugs, vaccines and medical devices, epidemiological research and laboratory based research (1, 2,3). However, as medical advancements take place and new medical technologies develop, the ethical complexities and contentions increase. For example, the understanding of risk vs benefit becomes blurred, there are conflicts between the advancement of science for the generation of new knowledge and individual risk and harm that a person might unknowingly go through, the clash between individual rights and personal interests versus public good and societal benefit. This has occurred with genetic research, personalised medicine, biobanks, and stem cell treatment and research, among others. (4,5,6,7)

**Ethical issues with biomedical research and Public outcry**

Historically, ethical guidelines developed after critical unethical events took place and resulted in public outcry. In 1930, the Lübeck disaster where 72 deaths occurred when 251 neonates were orally given three doses of the new Bacille Calmette–Guérin (BCG) anti tuberculosis (TB) vaccine contaminated with Mycobacterium tuberculosis drew public attention on medical experimentation on human beings and resulted in widespread criticism of medical professionals (8). The Reich Health Council Regulations (1931) were formulated in response to this (9). Nazi experimentation, including on infectious agents, in concentration camps led to the formulation of the Nuremberg Code in 1948. Again, the Tuskeegee study among black Americans, resulted in the setting up of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1974 and the Belmont Report in 1979 (10).

**The purpose of public engagement**

Interactions with the public on biomedical research, the benefits of participation, and the rules and bioethical guidelines that exist to protect their interests will likely create a more empowered public. This enables a wider base of governance of biomedical research and a greater accountability to society. (11) It is also important that ethics regulations evolve ‘bottom up’ and are not exclusively ‘expert based’ as the latter risks being “one-sided, biased or ideological—thus illegitimate” (12). Listening to the voices of the people also ensures that the notion of ‘public good’ encompasses multiple perspectives and standpoints. A key outcome of public engagement is a greater transparency of purpose and procedures, the ability to understand and to predict ground level problems at the individual and societal levels, identification of issues of vulnerability and methods to address them (13), addressing of fears and concerns of possible risks of participation in biomedical research and most importantly the building of trust between the scientific community and the public (14). Public engagement thus improves people’s participation, trust and confidence in the researcher, and understanding of the safeguards that exist. Public engagement in the development of the rules and bioethical guidelines that protect their interests, also establishes the public as a key stakeholder. (15)

Deliberative public engagement is also recommended for policy development in contested ethical areas. (16). This is not new. At the time of the BCG vaccine trials in Germany, Ludwig Fleck, a medical microbiologist and a philosopher of science, wrote extensively on the dilemmas of modern medical experimentation on human beings and the wellbeing of individuals. His approach was different from the existing approach of scientific reasoning and ethical regulations. He attempted to promote a more democratic understanding of science, the initiation of ‘thought collectives’ to deliberate scientific advancements of the time and to ensure a ‘public information campaign’ where scientific facts and uncertainties (in this case the controversies on the BCG vaccine) were informed to people (17). At the heart of Fleck’s arguments was the idea of the strong social dependence of all knowledge.

**What are public concerns with biomedical research?**

The general public in developing countries, especially communities with limited familiarity with English, do not comprehend the word ‘research’ (14; 18,19) and this often translates variably in local languages. Thus, an encounter with a physician is typically perceived as therapy. “Therapeutic misconception” therefore results in a low appreciation of the risks involved in experimental interventions (20). This is compounded by the trusting patient-doctor relationship, the paternalistic approach of physicians towards their patients and the power imbalance in the encounter. This, of course, reflects the norms and values of the culture and the society in which this encounter is embedded (21).

Lay people with some knowledge of medical research, even in India, have expressed their concerns about things going wrong, about the misuse of research, of the motives of the doctor-researcher, commercial involvement and commercial exploitation of research (14). The process of taking informed consent which is expected to empower research participants and respect their autonomy in choosing whether to participate or not, was seen by the public as protecting the interest of the doctor and the hospital more than their interests. (14). Persons from the lower socio-economic strata also feared anything given ‘free’, as free was associated with poor quality and doubtful intent. (14) Participants of research are also fearful that they will be forgotten after the research is completed, and that findings which might concern them or their children will not be shared with them. (22,23,24).

**Uncertainties in the context of Controlled Human Infection Model (CHIM) studies**

The purpose of a CHIM study is to intentionally infect healthy human volunteers and cause disease, thus, *harm*. A CHIM study would, therefore, be of greater risk than most other interventions (25). This also appears to fly in the face of the principle “*primum non nocere*” i.e. “first, do no harm,” also embodied in Principlism as “non-maleficence”. People conducting CHIM studies attempt to reduce risk through several means – they use well characterised strains for which the clinical course is generally well understood and for which there are effective treatments and also target healthy volunteers who are least likely to develop problems. However, this is not always possible. For instance, in the case of the Zika and E-bola virus infections, there are no known cures and the treatment is only symptomatic. Sometimes, infections may be associated with rare but significant complications. As an example, in the case of Zika virus there is the possibility of acquiring Guillain-Barre syndrome (GBS), a severe neurological disorder due to immunological problems caused by the Zika virus. (26) In these situations, the grading of risk will understandably be higher.

Some of the concerns about CHIM studies are a result of abuses that have occurred historically, some involving scientists of considerable repute. Armauer Hansen, for instance, the discoverer of M. *leprae* tried to inoculate the eye of a woman with material drawn from leprosy patient without her consent, in attempt to demonstrate Koch’s postulates (27). Albert Neisser, the second most celebrated German scientist (after Koch) at the time, and the discoverer of N. *gonorrhea*, injected women prostitutes with serum from those suffering with syphilis in an attempt to evaluate the efficacy of serum therapy in syphilis. These and other historical episodes contributed to an overwhelming fear of exploitation, and a sense that such research was unnatural and unethical (28). It is a fact that these episodes, unacceptable as they were, strengthened the resolve of people and researchers to prevent unethical research. Thus, Albert Neisser’s experiment were followed by the Prussian Directive, which emphasised informed consent, the protection of minors, and the need for experimentation to be done only by competent people. In this context, we now have better safeguards against unethical research than existed before.

Another relevant concern in CHIM studies is that of the volunteer comprehending the process of getting infected, developing low risk infection, the importance of confinement, reporting of symptoms and adherence to treatment. This requires a paradigm shift from informed, legalistic consent to empowered, understood consent. The fact that populations may be illiterate or poorly educated, belong to socially disadvantaged communities, and even if educated have poor ‘health literacy’ are significant challenges. Yet, these may also be the populations where the diseases are most prevalent and which are most likely to benefit from the research. From an ideological point of view, CHIM studies, and their translatory products, may sometimes be seen as an inadequate salve for wider health issues such as sanitation, clean drinking water, and improved food hygiene and nutritional practices, among others. While proponents of CHIM studies will argue that their studies do not offset the need or desire to address the social determinants of health, opponents will see these studies as doing precisely that – promoting immediate focussed solutions at the expense of longer, broader benefits.

The ultimate aim of a CHIM or challenge study is to make drug development pathways more efficient, less costly, and to test vaccine candidates in the country where the diseases are most prevalent and where patients are most likely to benefit from the intervention (29). The need for local CHIM studies is important since local/regional factors and the biological variability in different populations can alter host-pathogen dynamics, and make extrapolations of results from one population to another more difficult. The assessment of preliminary drug or vaccine efficacy could show that a vaccine candidate is likely to be ineffective thereby preventing unnecessary exposure of thousands of people in large Phase III trials.

There are specific uncertainties or ethical dilemmas for CHIMs.

1. An Individual is put at low, medium or high risk, with no direct individual benefit.
2. In the infectious state, the community may also be exposed to risk.
3. Several unknowns such as the duration of the infectious state, the modes of infection etc., make the period of quarantine difficult to define. Extended quarantine raises an ethical issue of prolonged, unnecessary confinement and shorter quarantines could enhance risk to family and social circles.
4. In the context of India and other developing country settings, there is a need to identify a true ‘volunteer’? Among other issues, the following may be important considerations:

* Someone who comprehends the risk and will follow the controlled regimen?
* Someone with sufficient health literacy who can consent to the risk?
* Someone who comes from the setting where the infection is generally prevalent?
* Someone healthy? How many will have to be screened– clinically and serologically, to arrive at the desired participant?
* Someone who can question freely the physician / researcher without fear, during the consent process

1. Compensation needs to be fair but not coercive. Would disclosure of compensation be an inducement for a healthy volunteer?
2. The study of the infective agent and its control needs to be of extreme public health / national health importance. Who makes this decision? The purpose of social benefit / public health/ greater good needs to be truly understood? Do the ends justify the means? Is it right to volunteer?

There is scarce bioethical literature currently available to guide researchers and research ethics committees in navigating the complex ethical issues of purposefully infecting healthy volunteers. The scholarly article by Bambery et al in 2016, suggests four requirements for human challenge studies to be ethical “(i) conduct independent expert reviews, including systematic reviews; (ii) ensure a publicly available rationale for the research; (iii) implement measures to protect the public from the spread of infection beyond the research setting; and (iv) develop a new system for compensation for harm” (30).

**Public engagement in the context of CHIMs**

The main objective of public engagement in the context of CHIMs is for all the stakeholders involved to understand each other and for all to understand the concerns and doubts and expectations of the key stakeholder which is the public. This will ensure that the ethical guidelines for CHIM studies in India, take into consideration the lived experiences and beliefs of communities in India. It will also not limit the construct of ethics to individuals but include a social component as CHIM studies have a public health component which needs public deliberation. Not only will this be in the public interest but it will also help the researchers in the acceptance, participation and understanding of CHIM studies and continuity in the generation of knowledge. The HPV vaccine trials in India show that any procedural or ethical lapses result in high levels of mistrust among the public and the medical researcher / medical community, (31,32) and a stoppage of the research.

Public engagement is desirable at three levels:

1. Evaluation of the ‘public voice’ through in-depth interviews with different sections of society, focussed group discussions with homogenous groups of people on the key ethical areas and public opinion surveys
2. Public education and advocacy where technical information on the purpose of CHIM studies, the inability to do such studies in animals or *in vitro*, and the roles of ethics committees as supervisory and regulatory bodies, in lay person’s language without being simplistic.
3. Public deliberation through town hall meetings / citizen juries / science cafes (similar to Fleck’s ‘thought collectives’) where the subject experts present the purpose, procedures and other scientific facts about a CHIM study as well as areas that are uncertain, followed by small group deliberation on specific questions. This allows for development of consensus as well as debate about contentious issues. Public deliberation is a structured process and an optimal methodology for discussion of newer areas and practices in health research. It allows for informed opinions, engagement in debate and arrival at collective decisions. (16, 33, 34) It goes beyond a process of symbolic consultation, and fits in well with Rawl’s publicity principle and his notion of “reasonable citizens.”

In addition, specific CHIM studies will benefit from ‘multi-stakeholder regulatory structures’ which have been used in other contexts to ensure transparency and accountability. (11)

Public engagement is not without its issues. Some may question whether the Indian public is ready for this highly engaged mode of working with scientists, doctors and government regulators, whether Ethics Committees are ready to modify their functioning to take on a more engaged mode of working with the public, and whether government agencies and funders of such research will invest the time and money for public engagement? These questions, while relevant, cannot be reasons for non-engagement with the public.

A vibrant public, aware of its rights, and of medical advancements aimed at public good, as well as the opportunities to engage with regulators and the researcher community, is not a threat but critical to ensure not only the acceptance and sustainability of research but a formulation of an inclusive ethics that values the public voice.

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