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View point

# Ethics & utility of controlled human infection studies (CHIS) in low- & middle-income countries

Controlled human infection studies (CHIS) having grown more common in the recent decades, the Indian Council of Medical Research (ICMR) released in 2023 the draft guidelines for such research in the country. The guidelines drew criticism from some activists and experts as premature[1-3]. While we agree with some of the critiques put forth, we also believe that the guideline fails to account for the full spectrum of scientific benefits from CHIS. While the exact mechanism of how India should best prepare for CHIS are outside the scope of this paper, we argue that the successful use of malaria CHIS in low- and middle-income countries (LMICs) with less robust scientific, medical, and ethics infrastructure provides evidence that some CHIS could still be conducted ethically in India and countries like it in the very near future with due caution and preparation.

## Purpose and utility of CHIS

CHIS, also called human challenge studies or controlled human infection model (CHIM) studies, involve the deliberate exposure of human research participants to a pathogen, usually in order to test a vaccine or a drug, and often as a means to identify the most promising candidates for further testing. These can also provide unique insights into a disease and into human immune responses, generating additional benefits outside of the immediate testing of a given vaccine or drug[4].

CHIS can be scientifically useful because these give researchers control over and hence provide knowledge of the exact circumstances of infection (*e.g.*, its precise dosage and timing). These also enable rapid generation of data that may otherwise be impossible to gather efficiently with a small number of participants. While CHIS may represent imperfect models of our complex reality, these have nevertheless been employed for the development of countermeasures for numerous diseases, often to very substantial effect[4].

In recent decades, CHIS have generally been conducted to high ethical, scientific, and safety standards. Since 1980, well over 10,000 participants have been challenged in CHIS across the world involving dozens of pathogens, and not one death has been recorded[5]. CHIS are not done using pathogens likely to cause permanent disability or death, and in the modern era these are performed exclusively on consenting, informed, healthy adult participants screened to ensure that they are not at high risk of any serious complications. As with all types of medical research, CHIS can be done ethically or unethically. While CHIS involve unique considerations and precautions, the fundamental ethical requirements of human participant research can still be met[6].

*Controlled human malaria infection (CHMI) studies*: CHIS involving *Plasmodium falciparum* rank among the most common types of CHIS since the 1980s[5], and have become integral to the malaria vaccine development process, facilitating greater scientific understanding of the disease and accelerated clinical testing of vaccine candidates[7-10]. These CHMI studies demonstrate how CHIS can be ethically deployed in and for the benefit of LMICs, potentially including India.

Mirroring other CHIS, one of the main benefits of CHMI is speed. A CHMI study can typically provide an initial assessment of vaccine efficacy or another anti-malaria product in as little as a few weeks[11]. Even accounting for recruitment time and other factors, a well-run CHMI can conclude much faster than a similar well-run field trial in malaria-endemic areas[11]. Thus, failed vaccine candidates can be quickly eliminated from consideration, with time and resources instead shifted towards the more promising options.

Both malaria vaccines approved by the WHO as of 2024, RTS,S and R21, had employed multiple

CHMIs for their development[4,10,12]. CHMIs enabled the relatively rapid evaluation of different doses, schedules, and adjuvants for RTS,S[4,12]. Sauerwein *et al*.[10] argued that absent CHMI studies, the RTS,S vaccine would 'almost certainly never have been developed'. CHMI were probably similarly crucial for R21, as three CHMI involving this vaccine were performed and registered (ClinicalTrials.gov: NCT02572388, NCT02905019, and NCT03970993).

Though ethically complex and requiring careful consideration, the harms to the willing participants in CHMIs are manageable and transient. These harms mostly entail contraction of malaria and/or side effects of the malaria treatments provided for free. While not trivial, such harms are explained to participants in the informed consent process and are typically evaluated beforehand by ethics review boards at the respective institutions running CHMIs. A recent systematic review[5] found only seven (0.6%) unexpected severe adverse events (SAEs) out of 1,129 people challenged in CHMI studies from 1980 to 2021. Most were mild, such as brief hospitalization for chest pain that resolved spontaneously, and none involved long-term disability or death[5].

Although useful, CHMI studies, like all CHIS, have limitations. Owing to their smaller sample size, these cannot fully assess the safety and efficacy of a given intervention, which must be confirmed in final, phase III field studies[4]. CHMI vaccine trials conducted among malaria-naive participants in non-endemic settings have shown higher vaccine efficacy than in endemic settings where malaria vaccines are actually intended for use[4]. This is one of the reasons CHMIs are now being conducted in endemic areas, which are overwhelmingly in LMICs.

*Expanding CHIS in India and similar LMICs*: To date, a vast majority of CHIS have been performed in high-income countries (HICs), though in recent years these have begun in LMICs as well with support from existing European and North American research centres[8,13,14]. Several benefits arise distinctively from the use of CHIS in LMICs. Many CHIS use pathogens that are not endemic in industrialized nations; relying on adults more similar to the ultimate target populations for related interventions can keep the results pertinent to target use[9,15]. Conducting CHIS and other early-phase research in LMICs can also build scientific capacity in these nations[9,15,16].

For some diseases, such as malaria, CHIS may be less risky or burdensome to the participants in LMICs compared to participants from non-endemic regions who have not built partial immunity to the disease[13]. Depending on the disease, CHIS in endemic areas could also confer natural or vaccine-borne immunity against future infections[17].

Qualitative studies of CHMIs in Africa strongly suggest that with careful community consultation and planning some CHIS are feasible and ethical in LMICs; these also provide a blueprint for addressing common issues that may arise as CHMIs (and other CHIS models) in further LMICs[16,18,19]. Still, differing regulatory, legal, cultural, and socioeconomic circumstances warrant additional care for CHIS in LMICs compared to industrialized countries.

*Preventing irresponsible CHIS in India and other LMICs*: Concerns over ethics dumping — the export of unethical research from HICs where it would not withstand regulatory and ethics oversight — have also been expressed about the prospect of CHIS in LMICs and should be taken seriously, perhaps representing a reason to indefinitely postpone these trials until India has western-level infrastructure of ethics oversight of human participant research[3]. We argue, however, that given the apparent successes of CHMI in Africa and the prospect of boosting Indian scientific capacity and contributing to research against nationally relevant infectious diseases, there is strong reason to believe CHIS can be undertaken in India in at least some form sooner rather than later.

First, international collaboration and funding for CHIS in India would be a prerequisite for the first CHIS in the country, and such studies would need to pass ethics review in their respective institutions similar to HICs. CHIS are also particularly compatible with multi-site testing[20], so further assurance could come from developing a uniform protocol with some percentage of participants in HICs.

Second, by doing CHIS, more can be learned about what is necessary in the Indian context to perfect regulation and oversight later on. Further protections can then be proposed by future scholarship in response to any additional considerations that become apparent in such early CHIS, as researchers in Kenya, for example, have done[14].

Third, the aforementioned apparent success of CHMI in African countries, which have been conducted

without a fully matured ethics and regulatory oversight mechanisms for such complex studies, suggests that CHIS in some form for some infections could be successful in India soon enough.

Fourth, CHIS for relatively mild or manageable infections like malaria should clearly be treated with somewhat less caution and trepidation than ones for more dangerous pathogens. Even for those retaining some scepticism of the initial guidelines drafted by ICMR, malaria should serve as an example of a disease for which CHIS could be possible. To postpone all CHIS in India pending perfect regulatory formulation would be unnecessarily broad. Differently put, it is precisely the need for improvements to the subcontinent's study oversight system that weighs in favour of the opportunity for expanded, collaborative scientific research. Excessive deferral would carry costs for Indian technical and scientific capacity as well as the people of India who could stand to benefit from the scientific knowledge gained.

*Payment to CHIS participants in LMICs like India*: Some critics and commentators in India are especially concerned with the prospect of participants in a CHIS joining primarily for financial benefit[2,21], an issue commonly expressed about medical research in LMICs[22].

Though well-intended, the notion that a desire for compensation is a reliable indicator of potential exploitation is mistaken (as is the related idea that altruism is mutually exclusive with a desire to be compensated fairly). Underpayment can be ethically problematic as well since participants deserve fair compensation for the inconvenience and discomfort they take upon themselves to advance medicine.

Notably, published literature on CHIS in LMICs shows that even relatively substantial sums of money compared to national per capita income did not impair the ability to conceptualize key risks[14,18,23]. This accords with a long history of research in HICs failing to identify cases where participants were unable to assess potential risks of medical research in the face of compensation (though other issues, such as incentivizing deception, may arise)[24-28].

*Moving forward in India with CHIS*: CHIS represent complex biomedical research endeavours, and LMICs rarely have the capacity to launch CHIS from the ground up, a concern also expressed by stakeholders in India[29]. Indeed, notwithstanding improvements to Indian regulatory oversight over the past several years, substantial progress remains necessary[30].

From the example of successful malaria CHIS, however, careful consultation and planning can see the rollout of at least some CHIS in even more resource-constrained settings. Pairing CHIS with established institutions and investigators abroad and involving their ethics oversight processes, as has been done with CHIS in Africa for malaria and pneumococcus vaccines[14,16], could enable the gradual build-up of Indian institutional capacity to conduct these and other, more complex studies more independently. Reportedly, doing so in Africa allowed local regulators to gradually familiarise themselves with the technical and scientific requirements of CHIS and enabled technology and knowledge transfer to domestic sources[31]. India possesses greater present scientific and technical capacity than the African countries currently conducting CHIS, but could similarly benefit from the training and knowledge transfer that initial CHIS collaborations with institutions from HICs would involve.

Thus, Indian research oversight and clinical trial capacity can initially be strengthened with established or lower-intensity CHIS, such as for malaria. The CHMI examples show that institutional perfection in LMICs is not a prerequisite to conduct such studies ethically and safely.

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