Indian Council of Medical Research

POLICY STATEMENT FOR THE ETHICAL CONDUCT OF CONTROLLED HUMAN INFECTION STUDIES (CHIS) IN INDIA 2023

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ICMR Bioethics Unit

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The central image features pathogens securely held within the gloved hands of a medical professional, symbolizing control. The bottom picture portrays a diagrammatic representation of a participant receiving a vaccine administered by a medical professional. More humans are shown around them in concentric circles. This entire scene is encapsulated within a bubble, symbolizing a controlled environment.

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ICMR POLICY STATEMENT
ON
THE ETHICAL CONDUCT OF CONTROLLED HUMAN INFECTION STUDIES (CHIS) IN INDIA
2023

सत्यमेव जयते

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सचिव, भारत सरकार
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स्वास्थ्य एवं परिवार कल्याण मंत्रालय एवं
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Secretary, Government of India
Department of Health Research
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Director-General
Indian Council of Medical Research

FOREWORD

In a world increasingly challenged by emerging and recurrent infectious diseases, Controlled Human Infection Studies (CHIS) have emerged as a promising research method, shedding light on disease pathogenesis and aiding in the selection of the most promising therapeutic agents. However, the intricate ethical dimensions of CHIS, entailing the deliberate exposure of pathogens to healthy volunteers, cannot be overstated. To address this, ICMR presents the "ICMR Policy Statement on the Ethical Conduct of Controlled Human Infection Studies (CHIS) in India, 2023".

This policy statement provides a comprehensive and standardized framework for the conduct of CHIS in India with a strong emphasis on ethical and scientific considerations. It marks a significant stride in the realm of biomedical research, offering a coherent blueprint to researchers and institutions conducting these studies that hold the potential to reform our approach to the prevention and treatment of infectious diseases, which was meticulously drafted through the collaborative efforts of experts from various fields with the aim of harmonizing the potential benefits of CHIS with the ethical challenges and inherent risks.

ICMR firmly believes that this policy statement will stand as an invaluable resource for researchers, ethics committees, sponsors, and all other stakeholders engaged in the conduct of CHIS in India.

Rajiv Bahl

(Rajiv Bahl)

New Delhi
6 November 2023

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This document is dedicated to the loving memory of **Dr. Vasantha Muthuswamy,** 12 July 1948 - 21 February 2023.

She served as the Chairperson of ICMR-Central Ethics Committee on Human Research (CECHR), 2020-2023 and also held the position of Senior Deputy Director General (Scientist G) and Chief of Division of Basic Medical Sciences, Traditional Medicine & Bioethics and Division of Reproductive Health & Nutrition at ICMR HQ until her retirement in 2008.

Her contributions to the field of Ethics of Biomedical and Health Research will be remembered.

"We'll be seeing you in all the old familiar places that this heart of ours embraces all day through."

~ICMR Bioethics Unit

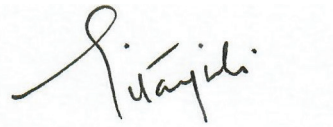
PREFACE

The “ICMR Policy Statement on the Ethical Conduct of Controlled Human Infection Studies (CHIS) in India, 2023” has been developed under the guidance of Dr. Rajiv Bahl, Director General, Indian Council of Medical Research (ICMR) and Secretary, Department of Health Research, Ministry of Health and Family Welfare, Government of India. It shows our commitment to promoting the ethical conduct of research and the protection of participants while advancing scientific knowledge responsibly. This document will guide researchers, sponsors, institutions and other stakeholders involved in reviewing or conducting CHIS. The unique research design of introducing infection in the human body to study diseases and treatment modalities warrants additional safeguards in order to ensure the protection of research participants. The document provides a comprehensive ethical framework, for the conduct of research and an ethics review, covering various aspects of CHIS which includes participant selection, ensuring local and cultural relevance, building public trust, complying with regulations, optimizing research outcomes, emphasizing transparency, accountability and adherence to ethical principles.

The preparation of this policy statement involved meticulous efforts and collective expertise of the members of the Expert Advisory Committee, who have brainstormed and invested significant efforts to ensure that this document meets the highest standards of comprehensiveness, current best ethical practices and scientific rigor. Their expertise, combined with invaluable insights from national and international peer reviewers, commentators participating in expert meetings, workshops and public consultations has resulted in a document addressing the ethical intricacies of CHIS which acknowledges our unique socio-cultural and economic context. We extend our heartfelt gratitude to all experts, reviewers and commentators for their inputs.

Along with them, we thank the scientific and support staff of the ICMR Bioethics Unit, especially Dr. Elna Paul Chalisserry, who provided assistance in the preparation of the policy document.

This national policy is poised to serve as a guide for researchers and ethics committees not only in India but we hope that this will be referred to widely and will offer suitable measures for the protection of research participants.



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1. INTRODUCTION

Controlled Human Infection Studies (CHIS) involve a research design that intentionally exposes healthy human participants to a specific pathogen or infectious agent, either in its wild type or in its attenuated form, under controlled conditions following stringent protocols. Similar studies have been conducted for several decades and yet their full potential remains largely unexploited. These studies may be employed to establish Controlled Human Infection Models (CHIM) aimed to assess vaccines, treatment modalities and accelerate research through enhanced insights into the disease process in humans. In contrast to lengthier natural infection studies, these studies may offer the advantages of quickly obtaining data and delivering accelerated results with smaller sample sizes. Regardless, these studies raise a plethora of ethical concerns mainly related to "the deliberate exposure of a human being to an infection." The deterrents to conducting these studies include technical, clinical, ethical and legal contentions, amid unique socio-cultural contexts in India. Therefore, their conduct requires a more careful deliberative review process to ensure local relevance, public benefit, fair processes, rigorous ethical oversight and all possible safeguards to protect the study participants from harm.

In recent years, both developed as well as developing countries have conducted CHIS for diseases such as malaria, influenza, dengue fever, typhoid and cholera. WHO has provided detailed guidance documents on ethical considerations for the conduct of CHIS. These studies are yet to begin in India and this policy statement intends to address the ethical issues arising around the conduct of CHIS in India. This statement is to be read in conjunction with the ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017 and is relevant to all stakeholders involved in the planning, conducting, reviewing or monitoring of CHIS.

2. SOCIAL VALUE

India suffers from a high burden of morbidity and mortality from infectious diseases, which contributes to about 30% of the total disease burden in the country. These studies offer an opportunity to provide unique insights into the pathogenesis of infectious diseases in highly exposed populations to accelerate the development of novel medical interventions. In the Indian context, CHIS could be a valuable research tool in bringing effective interventions for reducing disease burden in a timely manner. Further, CHIS can add social value in supporting public health response to diseases of concern, improved pandemic preparedness, community empowerment, economic advantage and assisting timely healthcare decision-making.

2.1. Obtaining a better understanding of infectious diseases by closely monitoring the development and progression of an infectious disease from its earliest stages including symptoms, incubation periods and immune responses, thereby contributing to the development of improved diagnostic methods and treatments.

2.2. Achieving immune response data which is required for early vaccine development by exposing only a limited number of participants to the pathogens.

2.3. Accelerating product development for diseases that are of national interest by obtaining outcomes relevant to the local population, especially for endemic conditions and associated co-infection. CHIS in endemic regions allows studies to be interpreted in the same genetic background as the eventual target population. The studies can help to focus on locally significant diseases and promote the development of indigenous products, thereby effectively addressing public health concerns.

2.4. Possibility of determining the minimum required dose of a drug (for protection) or of vaccine (for immunization) within a shorter time frame.

2.5. Developing interventions at lower costs and de-risking the process by down-selecting candidates that are ineffective or unsafe before they are tested in large numbers in Phase III trials.

2.6. Contributing towards building state-of-the-art facilities and local research capacities in clinical and laboratory diagnostics at global standards.

3. LIMITATIONS

CHIS come with a set of challenges and limitations, mainly with the safety of participants being a major concern due to the nature of risks involved to study participants.

3.1. Data produced from CHIS may have limited generalizability due to the testing carried out in highly controlled conditions and the often homogenous nature of participants recruited in small numbers limit the statistical power. The small numbers may not represent general populations and thereby lead to bias in the outcome. Hence, CHIS may warrant more studies and it does not necessarily eliminate the need for large Phase III trials.

3.2. CHIS may provide short-term data, making it challenging to assess the long-term effects of infections and treatments and there may be unknown risks associated.

3.3. Use of attenuated pathogens or specific well-characterized strains selected for safety and tested in a laboratory setting may not accurately represent the behavior of wild pathogens in a natural infection setting. Thus, the human immune responses to infections can vary greatly from the response induced by a wild-type or attenuated pathogen.

3.4. Determining clear and meaningful endpoints for CHIS can be challenging, impacting the utility of the model or the interpretation of results.

3.5. Further, the method has a limited scope since it can only study a select few pathogens, thereby restricting its applicability.

4. SCOPE AND OBJECTIVES

4.1. To identify the ethical considerations around the conduct of CHIS while ensuring the protection of the safety, rights and well-being of research participants.

4.2. To provide a framework to the ethics committees (ECs) involved in reviewing CHIS.

5. TECHNICAL CONSIDERATIONS

5.1. Challenge Studies

CHIS are conducted for testing therapeutics or vaccines typically in two stages, also, considered as two types of studies.

5.1.1. Controlled Human Infection- development studies:

In the first stage, when testing a new drug, healthy human volunteers are given wild strain/ attenuated pathogen in order to induce an infection or disease, usually mild and self-limiting or easily treatable. This process is known as the development of a Controlled Human Infection Model (CHIM) for that disease. Thereafter, the standardization of the Infection model is required to define appropriate clinical/ lab end points. This phase will also allow understanding the disease process and pathophysiology in the endemic population and identify the dose/ route/ appropriate vector, etc. required for developing a robust infection model. This standardization may require to be done a few times before a reliable infection model is available for use.

5.1.2. Controlled Human Infection- testing studies:

In the second stage, the participants are randomized, often with double blinding, to receive either the new drug or the currently available drug (or, if no treatment is available, a placebo). The two arms are then compared to test the 'pathogen clearance time' using molecular biology techniques or drug's capacity to treat the infection caused by the challenge strain.

5.1.3. In the case of a vaccine study, the process differs as the research participants are randomized to receive either the test vaccine or a comparator (currently available vaccine/placebo) and later introduced with the wild strain/ highly attenuated infective pathogen. The two arms are then compared to study the efficacy of the vaccine tested. The clinical endpoints need to be carefully defined in order to get information on the efficacy of the preventive approach.

5.2. Challenge Strain

The choice of challenge strains should be relevant to the objective of the study and guided by considerations of safety (causing minimal harm), availability and cost-effectiveness.

5.2.1. Use of well-characterized strains that have been previously used in similar studies is encouraged since they ensure consistency and allow reliable comparisons.

5.2.2. The development of the challenge strain should adhere to current Good Manufacturing Practices (cGMP) and other applicable guidelines.[a] The challenge strain should be manufactured using a reliable process, according to Good Laboratory Practice (GLP) and following local and international laboratory guidelines and standards (i.e., Good Manufacturing Practice (GMP); International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH); or International Organization for Standardization (ISO)). Quality will need to be continuously documented during the manufacturing process. Defined quality attributes should be taken into account and documented before quality control release. Manufacturing should take place in a designated laboratory, preventing contamination and allowing consistency in the final formulation by following a pre-defined manufacturing process and control testing. Stability during storage of the strain should be tested before release. A challenge strain might be manufactured by a third party, which should be qualified to do so. If this is the case, a product development report should be transferred to the clinical site before the use of the strain. It is recommended and often required to test the challenge strain for identity, purity, viability and stability before the start of the study.

5.2.3. The methods used in prior CHIS, where the model strain was characterized, could prove valuable. Broadly, details such as the source, clade/subtype etc. of the strain should be specified. The full sequence of the strain used should be provided – if it is a modified strain, for instance, with a specific gene deletion, it is essential to identify the process/method used for deletion and the validation process. The sequence of the strain should be known so that mutations in the future can be monitored.

5.2.4. When the same species is isolated during the course of infection, it should be characterized as thoroughly as possible, including the sequencing of part or whole genes or the whole genome. The plan for characterization should be included in the protocol.

[a] The use of the terms "current GMP" or "GMP-like" for the manufacturing of the challenge strain is prevalent in different settings across the world. In India, "GMP-like" may be practical but there are concerns related to lowering GMP standards. To avoid confusion and to ensure the protection of the research participants, the term "current GMP" is being used.

5.2.5. All microbiological/ virological/ parasitological testing should be conducted in accredited/ certified laboratories that have safety provisions in place to prevent transmission to personnel, the environment and/ or the community at large.

5.2.6. Biosecurity should be an important consideration and the use of Biosafety levels of labs would depend on the type of CHIS.

5.2.7. Irrespective of the required biosafety level, there should be strict adherence to the required laboratory design, personal protective equipment, biosafety equipment and implementation of Standard Microbiological Practices (SMP). Standard protocols, specifically trained personnel and Quality Assurance (QA) certificates, as applicable, are recommended for such studies.

5.2.8. The challenge strain may be naturally attenuated or genetically modified but should be intended to induce a response similar to or less than that of natural infection with an acceptable level of risk. The proposal should include results of preclinical or clinical studies conducted for other CHIS of the challenge agent. Additionally, Phase I data may be co-generated in the same study testing a product or should already be available and included in the proposal for certain types of studies. For example, in Malaria infection studies, it is very common to do combined Phase I/II studies.

5.2.9. Specific strains may require statutory approvals from various agencies, such as the Review Committee on Genetic Manipulation (RCGM) appointed by the Department of Biotechnology (DBT) for conducting research and development (R&D) activities and the Genetic Engineering Appraisal Committee (GEAC) appointed by the Ministry of Environment, Forest and Climate Change (MoEFCC) for large-scale use of genetically engineered strains. This is in accordance with the Regulations and Guidelines on Biosafety of Recombinant DNA Research & Biocontainment, 2017 and other guidelines issued by DBT from time to time.

5.2.10. Import or transfer of the challenge strain across national borders requires additional consideration and adherence to the existing regulatory framework and other applicable norms. Revised Simplified Procedures/ Guidelines on Import, Export and Exchange of Genetically Engineered (GE) organisms and products thereof for R&D purpose, 2020 vide DBT OM dated 17.01.2020 and other guidelines issued by DBT may be referred for R&D purposes in the process of CHIS strain development.

5.3. Study Plan

CHIS is a form of clinical research and the study protocol should include a scientifically sound research design, methodology, adequate sample size, intervention and control groups, rescue therapy and a plan for standardized statistical analysis capable of generating outcomes of public health value.

5.3.1. Scientific and research requirements would be unique to the disease under consideration. The study design should be disease-specific with clarity on the potential scientific benefits for translating findings into public health goals. It should address issues related to the disease itself, its diagnostics, proposed vaccine development and improved treatment modalities or preventive strategies for the future.

5.3.2. CHIS commonly employs Randomized Controlled Trials (RCTs) (often double-blinded) study designs. The advantage of CHIS is that, despite requiring a smaller sample size compared to conventional clinical trials, it can still yield meaningful differences between intervention and control groups. There should be clear-cut justification and supporting peer-reviewed literature and evidence used for determining the sample size for these studies.

5.3.3. CHIS are conducted on healthy volunteers and thus, the study protocol should clearly define the screening and selection criteria. In certain types of studies, the outcomes may be uncertain, however, the protocol must provide anticipated endpoints based on existing literature from natural infection studies, preclinical studies and/or animal studies or previous CHIS conducted elsewhere. These endpoints could include clinical symptoms, immunological responses or other measurable outcomes related to the specific pathogen or disease.

5.3.4. The methodology should outline the required steps, such as the procedures for inoculating the pathogen, the range of dosing (as applicable), laboratory investigations, immunological assays, assessment of clinical outcomes, monitoring and any follow-up procedures, as they may differ from pathogen to pathogen.

5.3.5. A rescue plan should be in place to address any complications or adverse events (AE) that may arise during the study. There must be predefined criteria for initiating appropriate medical interventions and providing the required medical management for the safety and well-being of the participants.

5.3.6. The interpretation of the results should be carried out with due consideration given to the unique methodology, potential confounding factors and limitations of the study.

5.4. Scientific Review

In view of the present limited knowledge and experience in CHIS, it is desirable to conduct a detailed scientific review prior to submission of the study protocol for an ethics review.

5.4.1. The scientific review must be undertaken by an expert review committee or through an independent peer-review process. It must receive approval from an appropriate committee that operates independently of the researchers/ sponsors supporting this research.

5.4.2. Academic institutions planning to engage in CHIS could appoint an expert committee (national/ international) specifically for this purpose. The committee could include independent subject experts, such as immunologists, infectious disease experts, microbiologists, epidemiologists or others as members who have the required expertise to review the scientific aspects of CHIS.

5.4.3. The comments and suggestions of the scientific committee should be duly incorporated into the study protocol before submitting it to the Ethics Committee for review.

5.4.4. Scientific considerations of CHIS would be disease-specific and must be duly deliberated upon so that the implications are understood. For examples, please see Table 1 below:

Table 1 : Disease-specific considerations for CHIS

Disease	Specific Considerations
Malaria	• The infection model may be developed either by inoculation of sporozoites via mosquito bite or by direct injection of sporozoites or Plasmodium-infected blood. • Considerations regarding the mode of transmission, possibility of relapse and latency differ based on whether the infection is *P. falciparum or P. vivax.* • Conduct of the CHIS requires trained staff, a consistent infection model with well-characterized strains, controlled access to infected participants, reliable and quick diagnostic methods and effective treatment. • Study should be facility-based to ensure access to participants and prevent exposure of mosquitoes to infected participants, particularly in non-endemic regions. • Clinical endpoints depend on the purpose of study and can include parasitemia detected by molecular methods or fever. • Procedure of rearing and infecting the vector to also be included if vector being used.

Disease	Specific Considerations
	• Sub-curative treatment should be provided in the middle of study to reduce morbidity but still allow transmission. Complete treatment to be provided at the end of the study.
Dengue	• Test for previous dengue exposure, with rigorous screening especially for frequent travellers living in non-endemic areas. • Lack of a known correlate of protection, complex and poorly understood disease pathogenesis, virus circulation resulting in varying disease severity and lack of a reliable animal model. • Potential enhanced risk of severe dengue in a previously exposed/ infected individual. • End point may be viremia or clinical symptoms and therefore requires in-patient facilities. • No known antiviral and possibility of severe disease. • Prevention of exposure of infected participants to mosquitoes.
Tuberculosis	• Concerns for safety arise when using wild-type ***M.tb*** as the infection cannot be reliably eradicated from an infected participant; treatment is prolonged (6 months) and toxic with potential for serious adverse events; and there is a potential risk of immunopathology with inadequate or complicated treatment options. • Risk of recurrent infection after treatment. • Challenge agent administration can be intradermal BCG/ modified BCG, modified ***M.tb*** or nebulized BCG/ oral route. • Determining endpoint may require a punch biopsy and the immunological response to ***M.tb*** can show variation between participants and can be altered by concurrent infections. • Risk of transmission to the community through nasopharyngeal route in the pulmonary model. • Airborne transmission and environmental contamination with the challenge agent require a protocol to demonstrate risk mitigation.
Typhoid	• Well-characterized susceptible strain of ***S. Typhi*** should be used as a challenge agent to avoid known complications of typhoid. • Design facilities for follow-up patients to provide intensive follow-up and care as needed and reduce third-party risk. • Endpoint may be blood culture positivity, fever or prolonged shedding of bacteria in stool; the protocol must define the trigger for antibiotic treatment. • Effluent treatment essential in resource-poor settings.

6. RESPONSIBLE CONDUCT OF RESEARCH

CHIS must be conducted with the highest level of scientific and ethical standards. This involves careful planning, coordination, monitoring and collaboration between various stakeholders.

6.1. Institutional Responsibilities

6.1.1. Rigorous background preparation is involved, and thus, institutions/centers with academic excellence that possess the necessary infrastructure, resources, budgets, space, facilities and skilled and motivated personnel to handle the complexities must undertake these studies.[b]

6.1.2. These sites must have an extensive prior experience in conducting clinical trials, with a proven record of academic excellence as well as tertiary-level clinical facilities. Provisions must be in place to closely follow-up and monitor participants.

6.1.3. If the study requires a closed setting, especially in cases where significant clinical symptoms are expected, it is essential to have emergency/ critical care provisions for participants and strategies in place to prevent the spread of infection.

6.1.4. Extra caution is required if the challenge strain is genetically modified and likely to mutate. Investigators must define mitigation measures in their study, especially if it involves ambulatory participants who will be allowed to live in the community for the study's duration, with the potential to transmit infection to third parties.

6.1.5. Clinical facilities and laboratories within the selected institutions should be accredited and enrolled in robust quality assurance programs. Regular audits and inspections should be conducted to ensure the highest standards of quality and patient safety are maintained.

6.1.6. Institutions must facilitate the review by the appropriate committees and obtain permission from relevant committees or agencies or regulatory bodies in India. These may include Institutional Scientific Review, Institutional Ethics Committee, Institutional Biosafety Committee (IBSC) (including infrastructure/ environment surveillance) and other relevant authorities as applicable, such as the Central Drugs Standard Control Organization (CDSCO) in the case of clinical trials.

[b] While commercial enterprises undertake CHIS in other countries, at present in India, only tertiary care medical institutions with academic excellence preferably centers of repute and standing (public or private not-for-profit) should undertake CHIS.

6.2. Responsibility of Researcher

6.2.1. The researcher, along with the study team, should be adequately qualified, trained and skilled and have prior experience in conducting clinical trials. They must receive updated training on guidelines for Good Clinical Practices (GCP) and ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017 along with other applicable guidelines and regulations. It would be useful if the research team has the opportunity to receive training/ exposure to ongoing CHIS in other parts of the world (offline/ online).

6.2.2. Researchers must ensure that, as per the study requirements, they adhere to the approved version of the protocol and documents and are compliant with relevant laws, regulations and guidelines. All aspects related to the conduct of the research must be properly documented and reported to the respective committees/ bodies/ agencies in a timely manner.

6.2.3. Administration of challenge strain should be carried out only by trained members of research team to ensure consistency of practice. These team members should have undergone supervised training to proficiently follow-up on procedures.

6.2.4. Research study must have an adequate budgetary provision in the protocol or insurance cover to provide the required resources for the conduct of CHIS and to meet untoward or unexpected adverse events. This includes costs for medical management, treatment, hospitalization, reimbursement of expenses, payment of compensation related to injury, ancillary care, etc.

6.2.5. Study team must have adequate capacity and resources available for close monitoring during the course of the study and for the long-term follow-up of participants.

6.2.6. Any adverse events that occur during the study must be reported promptly and accurate records should be maintained and available.

6.2.7. Study must be open to inspections and audits by regulatory authorities as per existing guidelines and all records should be made available to the relevant stakeholders.

6.2.8. Before a participant is discharged, it is important to ensure the infection is completely resolved. A certificate of “Complete Clearance of Infection” or for “Participation in CHIS” may be issued to the participant, if required, for specific diseases as this may have long-term implications, including the participant testing positive in view of the immune response generated during testing.

6.3. Conflict of Interest

6.3.1. As with other types of research, Conflicts of Interest (COI) can arise when researchers, sponsors or institutions have financial, professional or personal interests that could bias the study's objectivity and conduct, potentially impacting participant recruitment, informed consent and reporting of results.

6.3.2. Commercial business interests, if any, need to be declared in advance. CHIS may involve per-participant recruitment fees by the researcher, which should also be declared to the EC.

6.3.3. Declaration and management of these COIs are essential for scientific integrity and ethical standards. Hence, conflicts of interest of all kinds must be declared and managed by all stakeholders who undertake CHIS or are involved in its scientific or ethics review.

6.3.4. It is preferable that the institution should have proper policies in place for the declaration of COI by researchers, ethics committee members or even institutional authorities involved in decision-making for CHIS.

6.4. Collaboration and Data

6.4.1. Being a highly complex area of research, CHIS may require extensive collaborations at various levels, such as among researchers, institutions, organizations within or even between countries to bring in the requisite expertise to undertake these studies. Researchers new to CHIS may find it beneficial to collaborate with research institutions with more experience.

6.4.2. Collaboration can help improve outcomes, such as identifying ways for the study results to be carried forward and meaningfully translated into other studies wherever applicable (e.g., phase III vaccine trials). Collaborating researchers can work closely right from the planning to the implementation process throughout the study.

6.4.3. The research team must identify the terms of reference for collaboration, defining their roles and responsibilities under the agreed Memorandums of Understanding (MoUs) and Material Transfer Agreements (MTA). They must obtain the EC approval at collaborating institutions.

6.4.4. The data-sharing mechanisms can be defined and preferably a data-sharing policy should be prepared for the study in line with applicable regulations and ethical guidelines.

6.4.5. As with all clinical research, CHIS in India should be conducted only for diseases prevalent in the country. Collaborative research should not focus solely or mainly on diseases of concern in high-income countries when conducted in low/ middle-income settings, as these settings may not gain much from the outcomes/ results of such studies. This is needed to prevent ethics dumping.

6.4.6. CHIS may involve the collection of sensitive, identified and personal information. Information should be coded or anonymized to protect identity before sharing with collaborators/ other third parties. Access to such information must be limited to only relevant study personnel or regulatory authorities.

6.4.7. Researchers should strive to publish the results of the study, whether positive, inconclusive or negative, which may discuss the characterization of disease outcomes, long- term safety profiles and provide insights into the efficacy of interventions. The contribution of all stakeholders involved in CHIS must be duly acknowledged.

7. ETHICAL CONSIDERATIONS SPECIFIC TO CHIS

The intentional exposure of healthy participants to pathogens, even in a controlled environment, raises unique ethical concerns putting forth a need for additional safeguards and oversight.

7.1. Deliberate Infection

While such studies may yield valuable insights into the disease pathophysiology and potential treatments, intentional exposure to disease-causing agents or pathogens for developing a human infection model of disease is considered a contravention of the Hippocratic Oath and violates the "do no harm" ethical code for medical practitioners. This exposure to infection, owing to the methodology, has immediate effects due to the pathogen itself and also has a potential for long-term health-related consequences. The following steps could be followed:

7.1.1. To reduce ethical complexity when introducing CHIS for the first time in a new setting, such as India, it may be helpful to conduct studies with an existing model first, preferably one with self-established safety. Caution may also be warranted initially and steps should be planned to build confidence among researchers, ECs, regulators and the public. For example, the first CHIS may involve an established, relatively low-risk model, such as the rhinovirus, where illness is mild and self-limiting, or a controlled human malaria infection study, where the infection can be effectively treated with anti-malarial drugs. This approach could replicate a low-risk model as long as third-party risks could be managed. [c]

7.1.2. Participants should be provided with detailed information about the rationale and nature of the study, including the potential risks and benefits, expected endpoints, treatment plan, duration of infection clearance and measures to minimize risks and post-trial provisions. An assessment of the level of deliberate infection with expected and unexpected outcomes, its reversibility and a comprehensive risk mitigation plan must be in place.

7.1.3. The study plan should be developed with careful inclusion/ exclusion criteria, an appropriate duration of confinement, ways to minimize risk to third parties and plans for close monitoring of participants.

[c] The development of a new CHIM with a novel pathogen in India might not be advisable since it may involve less predictable and more uncertain risks, including those to third parties. In addition, starting with a higher risk CHIS such as influenza, which has limited treatment options may threaten public trust if one or more participants are harmed in the trial.

7.1.4. In the initial stages, CHIS should be undertaken for diseases that are self-limiting and treatable. However, in case of emergent reasons or a pandemic situation, detailed deliberations would be required to understand requirements and available options before CHIS can be allowed to be conducted. This may need extensive deliberations by the scientific and ethics committee and only be permitted after due deliberations at the highest/ national level before implementation.

7.2. Selection of Participants

The selection criteria for participants would be based on the needs of the study protocol, considering the high possibility of uncertain outcomes and identifying ways to avoid possible harm.

7.2.1. Participants should be healthy adults between the ages of 21 and 60 years, unless otherwise justified. A rigorous screening of the health parameters of participants is required to identify any pre-existing medical conditions. If an increase in risk is suspected, such participants should be clearly excluded from the study. [d]

7.2.2. Participants should be at least graduates (i.e., those who have completed a degree program at an educational institution, such as a college or university). This ensures they are mature enough to comprehend the research purpose, potential benefits, possible harm and are better placed to make an informed decision regarding their participation. [e]

7.2.3. The study team must adopt fair and transparent processes for recruitment. An open and transparent call for volunteers to join the study could be implemented. Transparent procedures should be in place, ensuring there is clearly no pressure or undue inducement on participants to give their acceptance for participation. [f]

[d] Even though an individual of 18 to 20 years of age could be a healthy adult eligible to give legal consent, the level of maturity to make complex decisions may be limited. It is desired that the person should be capable of understanding all the nuances. Besides inexperience, the threshold of risk-taking and hasty decision-making is common at this age and may compromise objective thinking.

[e] It is known that the opportunity to participate should be offered to everyone and formal education should not be equated with intelligence and comprehension. This clause may exclude a large section of literate individuals from enrollment. While education is important for improved understanding, higher levels of maturity and intellectual capacity can enhance the informed consent process, although they do not guarantee perfect comprehension.

[f] Undue inducement includes offering disproportionate benefits in cash or kind that compromise judgment, which may, in turn, lead to the acceptance of serious risks that threaten an individual's values or interests.

7.2.4. Researchers must consider participants; motives for taking part in CHIS, as these studies do not offer any direct health benefits to participants. The participants may participate due to a variety of reasons; for some, it could be altruism, involving a genuine desire to contribute to public health advancement, while for others, there could be other motivating factors such as money or fame. Regardless of the motive to participate, it is crucial to ensure that the participant fully understands the procedures and implications and that there is no undue inducement or coercion involved. The study team should provide detailed information and ensure a thorough understanding of the scientific aspects as well as social value of research, along with a complete understanding of the risks involved. The researchers must evaluate the nature of participants' motivation to participate to the extent possible. Researchers must exercise due care to ensure motivation, true understanding and free will to participate. [g]

7.2.5. The selection process should be unbiased with regard to gender, unless there are specific scientific reasons for gender-based restrictions in the proposed studies.

7.3. Vulnerability

Vulnerable individuals are those who have limited autonomy and are either relatively or absolutely incapable of safeguarding their own interests due to personal disability, environmental burdens, social injustice, a lack of power, understanding, or the ability to communicate or they may find themselves in situations that prevent them from doing so. Vulnerability can be categorized into two groups: inherent and situational. [h]

7.3.1. Inherent vulnerability refers to individuals who naturally possess these characteristics and are thus unable to protect their own interests in research. Consequently, any category of inherently vulnerable persons or groups, such as children, the elderly or persons with physical/ mental/ developmental disabilities should not be included in CHIS. Any research planned among elderly would require due caution and would need to be adequately justified.

[g] As of now, there are no specific tools available to measure a person's desire or motivation.Evaluating altruism is a contentious issue, even in conventional clinical trials and there are no objective assessment tools to measure it.

[h] In line with the principles of inclusion, it is important to involve individuals from all backgrounds. However, in the case of CHIS, where only a small number of participants are needed and there is no prospect of any direct benefit, a decision has been made to exclude vulnerable individuals or groups. However, If the objective of the study is specifically intended for a particular group, such as the elderly, additional considerations must be taken into account.

7.3.2. Women who are pregnant, breastfeeding or planning to conceive within the study period should be excluded from participation due to potential risks to both the mother and the developing fetus. Adequate counselling should be provided at the time of recruitment. If a female participant becomes pregnant during or shortly after the study, appropriate prenatal care must be administered and long-term follow-up is necessary.

7.3.3. Situational vulnerability, on the other hand, pertains to individuals who may experience diminished autonomy within certain specific situations, making it essential to safeguard their interests in research. This applies to subordinate, students or individuals lacking authority who work under researchers or employees directly reporting to researchers. It also extends to other groups, such as prisoners, marginalized populations or tribal communities, who may encounter situational vulnerability and thus should not be included in CHIS.

7.4. Benefits and Risks

While CHIS may be beneficial for science, the accompanying risks or harm (temporary or long term) to participants may be significant. It is therefore important for researchers, institution and ECs to undertake a robust assessment of benefits versus risks and consider this from the perspective of the participant to determine acceptable levels. Any potential challenges and risks that may arise during the research process should be proactively identified and addressed through appropriate risk mitigation strategies.

7.4.1. There may usually be no direct/ indirect individual benefits for participants in these studies, except for the opportunity to altruistically contribute to science. These studies offer the prospect for scientific advancement, future benefits and implications for public health.

7.4.2. In some types of research, there may be indirect advantages, such as referrals or other health services that may be made available, long term follow-up or laboratory investigations, ancillary care, counselling or other medical care or the small possibility of improved protection against future infections due to exposure to controlled doses of pathogens during participation.

7.4.3. On the other hand, participation in these studies may involve significant risks when participants are involved in CHIS or contribute to human disease models aimed at understanding disease progression, transmission and immune responses due to exposure to pathogens. Deliberate exposure of healthy participants to the pathogens raises ethical and moral concerns and may pose tremendous risks for conditions where there are no treatments or unknown outcomes.

7.4.4. Risks could not only be physical but also psychological or emotionally draining. CHIS may involve additional risks and discomforts due to the nature of research procedures involved.

7.4.5. Prolonged social isolation or separation from loved ones, as required for certain types of studies, may lead to psychological distress such as anxiety, loneliness or depression, affecting mental well-being. Appropriate counselling and psychological services should be provided. Plans for such studies should include psychological evaluation during screening to look for any past history of psychiatric illness and/ or anti-psychotic medications and individuals detected with such history should not be included in the study.

7.4.6. The researchers are responsible for reporting all AE and Serious Adverse Events (SAE) to the EC, sponsor, regulatory authorities as outlined in ICMR National Ethical Guidelines for Biomedical and Health Research involving Human Participants, 2017 and NDCT Rules, 2019.

7.4.7. CHIS may thus involve "double risks" – those arising from deliberate infection and those of conventional drug/ vaccine trials. All adverse effects – expected or unexpected – need to be managed and taken care of. The study budgets should cover all costs during and for a defined period after the study.

7.4.8. Cross-infections to third parties, such as team of researchers, healthcare workers, family members and household contacts, friends and the community at large or at the facility, could be a significant concern.

7.4.9. Environmental risks include the potential for unintentional pathogen release, containment failure, improper waste management and the risk of airborne transmission, which may result in environmental contamination and pose hazards to the surrounding community if not managed carefully.

7.5. Additional Safeguards

Researchers must make every effort to provide comfort and ensure the safety and psychological well-being of participants.

7.5.1. All in-patient participants should be provided with hygienically prepared healthy meals during the course of the study, preferably as per their cultural and dietary preferences. Basic hygiene amenities, such as clean water, sanitation facilities and other necessities, should be made available.

7.5.2. Where the nature of the study requires participants to be isolated, researchers should encourage regular communication between participants and their loved ones through appropriate channels, such as virtual meetings, phone calls or video conferences. Provisions for recreational and leisure activities, as well as the use of multimedia such as television, radio and music may be helpful to relieve stress and maintain a positive state of mind.

7.5.3. There should be honest communication and an explanation of procedures including expected physical responses and discomforts to the participants. Participants should have access to mental health professionals who can offer support and counseling throughout the study. There are possible harms related to contamination/ spread to the environment and utmost care may be required to protect against the same. This involves strict containment protocols, waste management procedures, monitoring and surveillance, community engagement and adherence to regulatory guidelines to ensure the safety of both research participants and the surrounding environment.

7.5.4. Healthcare workers are at a high risk of contracting and transmitting infections and therefore, must undergo regular health screening to rule out infection. All involved personnel must receive adequate training in infection control measures and be provided with the necessary protective equipment to protect themselves and prevent the spread of infections.

7.5.5. Family members and other visitors to the healthcare facility should also undergo screening to prevent the spread of infections. Visitors should receive equivalent infection control training and have access to facilities and equipment similar to healthcare personnel. Confinement and/ or the use of contraceptives to minimize risks to third parties must be ensured during infectious periods.

7.6. Informed Consent Process

Informed Consent refers to the process of full disclosure of the nature of the research and the participant's involvement in research, ensuring adequate competence, comprehension and voluntariness. The content of the informed consent *[See Annexure 1a, b]* should be in accordance with ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants 2017, along with the following additional considerations.

7.6.1. The Informed Consent form must include a statement explicitly stating that CHIS is a type of research study and provide a simplified explanation of this concept.

7.6.2. Researchers must invest sufficient time and effort to thoroughly explain the procedures, risks and benefits, particularly in situations where the complexity of the study design may hinder participants' comprehension. Participants may not fully grasp the nature of the research, potential risks and participation requirements. Therefore, it is crucial for the investigator to devote enough time and resources to communicate well and to assess an individual's capacity, voluntariness and motivation before obtaining informed consent.

7.6.3. The consent must be prepared in a simple form, manner and in a language considering the social and cultural contexts. This ensures a clear understanding of the purpose and procedures of the study, along with the anticipated risks and benefits. Participants must also receive information about available rescue treatments and procedures, if required. It is important for participants to know that the alternative to participation is choosing not to participate. Additionally, they may also be informed that they will receive a standard of care appropriate for the disease under study. Limitations, if any, should also be explained.

7.6.4. Participants must be given the opportunity to ask any questions and have sufficient time to engage in discussions with their family and friends and revert back if they want to before making a decision. This process may involve detailed one-to-one interactions and/ or small group discussions, including their immediate families, as required by the study, to ensure that participants gain a comprehensive understanding of all aspects of the study. Contact information should be made available to the participants for reaching out at any time. The decision to participate should be made only after enough time has been given to think over or discuss with family and friends, following a clear understanding of the study.

7.6.5. Researchers must ensure that there are no undue inducements or other factors that could influence thinking or decision-making processes. Investigators, the research team or any authority should refrain from engaging in any measures to influence or coerce a participant into an agreement.

7.6.6. Participants must be given the opportunity to make a voluntary or free choice regarding their agreement or disagreement to participate without any pressure, coercion or undue influence. They should also have sufficient time to discuss with family or friends before they make a decision regarding participation. The ICD process must be conducted with respect towards the study participants, their families or individual or communities involved.

7.6.7. A test of understanding must be planned for every study, consisting of an open-ended set of questions, to ensure that the study and the procedure involved are adequately comprehended *[See Annexure 2]*. Only those who are able to clear the test, demonstrating an adequate understanding, may be recruited. A record of the conducted test of understanding must be maintained, along with the record of informed consent process.

7.6.8. Researchers should inform and educate the participants about the risk of third-party transmission and additional infection control measures upon withdrawing from research. This information should be clearly mentioned in the consent form so that participants can fully understand and agree to comply with the infection control measures.

7.6.9. Informed consent form should clearly inform the consequences of withdrawal, if any, such as the potential transmission of disease to third parties. Consequently, the form should specify the circumstances in which withdrawal is permitted and when it is not, outline any potential restrictions for withdrawal and describe any quarantine measures, if needed.

7.6.10. Informed consent should be documented in writing. The process of obtaining consent and process must be recorded and the audio-visual tools should be used for the same. It is mandatory to appropriately record the complete process, including information provided, comprehension, discussion and signing of the consent after full understanding.[i]

Consent form elements and additional considerations are given in the following Table 2.

[i] Informed consent process, which includes the time spent explaining, discussing, answering queries and then signing the form, should be recorded. This is expected to improve the accountability and transparency of the consent process.

Table 2 : Elements of Informed Consent Form

Basic Elements
Statement about the research study
Purpose and procedures in simple language
Duration of participation and type of data collection, procedures and number of participants
Benefits and possible outcomes for individual/ family/ science
Foreseeable risks, inconveniences harms and mitigation plans
Privacy and confidentiality of identified information
Reimbursement of costs and payment for participation
Medical management/ compensation for related injuries/ insurance cover/ follow-up
Freedom to withdraw and the limitations
Contact Information of study team/ EC
Additional Considerations
Motivation to participate/ participant selection criteria/ altruism/ other factors
No undue pressure/ coercion/ influence
Third-party transmission/ potential risks and burden to individual and community/ environment
Possible need for confinement in some cases – details of duration, facilities etc.
Psycho-social support/ management/ counselling if any
Possibility of stigmatization/ long-term effects (for e.g., immune status)
Mandatory AV recording of the informed consent process
Test of understanding and comprehension
Storage and transfer of biological materials/ data
Post-study plan/ benefit sharing/ dissemination/ publication of results/ long term follow-up

7.7. Privacy & Confidentiality

Participation in CHIS may involve a risk of social stigmatization upon breach of confidentiality, which could have implications on participants' or their family's health and well-being. The study data may be sensitive and need to be protected to ensure its use is limited to the purposes of the study.

7.7.1. The degree of identifiability of the data collected significantly influences the level of privacy, confidentiality and potential risk to participants. Therefore, data should be collected with care and duly safeguarded. Only authorized personnel should have access to identified data. Researchers and institutions bear the responsibility to secure sensitive data to prevent any malicious use.

7.7.2. CHIS data would require longer-term storage (>15 years) and thus appropriate data protection measures must be in place and informed to participants prior to their recruitment in the study.

7.7.3. If identified data sets are to be published or shared with collaborators, appropriate permissions, consent and ethical approvals from relevant authorities, along with any other requirements to safeguard participants, must be in place.

7.7.4. If a participant wishes to share their individual story of participation through print, writing, video or social media, it could compromise anonymity. Efforts should be made to ensure that there is no overhype or undue publicity of unproven outcomes while the study is ongoing. Adequate counseling of participants may be carried out, with the aim of improving understanding and promoting mature handling of sensitivities. [j]

7.8. Payment for Participation

Participants must be paid a reasonable amount of money to cover their costs for time spent in screening, investigations, study procedures, loss of wages, any period of isolation and inconvenience incurred.

7.8.1. Any expenses incurred, such as transportation costs, should be reimbursed and payments can be planned on a pro-rata basis.

7.8.2. The protocol budgets must include the costs associated with payments to participants and reimbursements of expenses. The method of payment whether in phases or installments, before or after the study should be clearly mentioned and reviewed.

[j] In other settings, potential volunteers are offered the opportunity to connect with people who have previously volunteered for similar studies

7.8.3. The EC must review all payment reimbursements, whether in cash or kind, facilities as well as other provisions to determine what is reasonable. The EC should carefully assess the amounts involved in payment or reimbursements of incurred expenses to determine adequacy and appropriateness.

7.9. Study Monitoring

CHIS involves deliberate exposure to pathogens, thereby putting forth the need for robust independent monitoring. This monitoring may be carried out at different levels – self-assessment by researchers, oversight by institutional authorities, ECs, sponsors or by committees such as Data and Safety Monitoring Board (DSMB), Community Advisory Board (CAB) and also by the society, regulatory bodies and others as applicable. Monitoring methods could include time-to-time reports, continuing reviews, actual site visits, follow-up calls, regular inspections, audits and others.

7.9.1. The institution is responsible for ensuring robust conduct of research, compliance with guidelines and integrity in data collection methods and analysis. Researcher must undertake research as per the study protocol. Any deviations or violations must be promptly reported to the EC. Amendments, if any, require prior approvals from EC before implementation. Appropriate and close monitoring measures must be in place to ensure adherence to these standards.

7.9.2. The EC should ensure that the study protocol includes an appropriate plan for monitoring study participants.

7.9.3. Researchers must take all necessary precautions to prevent the spread of the pathogen beyond the study population to household contacts, the community and similar. However, in the event that a third party develops symptoms due to post-trial exposure by the participant, reporting to both institutional authorities and EC is mandatory. Additionally, arrangements for medical care must be made immediately.

7.9.4. Regular monitoring and audits planned by the Sponsors such as the DSMB, ECs, and regulators (if applicable) are essential to ensure the robustness of conduct of the study and the safety of research participants' rights, safety and well-being in research. EC may also conduct site visits if needed.

7.9.5. All AEs must be reported to the EC and the sponsor, as applicable, within the specified timelines as described for drug trials. All SAEs must be informed to the EC within 24 hours of knowledge through email or fax communication, including on non-working days. A report detailing how the SAE was related to the research must also be submitted to EC within 14 days.

7.10. Compensation for Research-Related Harm

The risks associated with participating in CHIS may be significant and there should be appropriate budgetary provisions to provide compensation in case of any research-related harm or injury to the participants.

7.10.1. Rule 43 of Chapter VI of the NDCT Rules, 2019 contains provisions for medical management and compensation in case of injury or death in clinical trials, Bioavailability (BA) or Bioequivalence (BE) studies. In case of death, the participant's dependents are entitled to financial compensation. Furthermore, all compensation provisions outlined in the NDCT Rules, 2019 are applicable in these cases.

7.10.2. For other academic studies or biomedical and health research, Chapter IV of the NDCT Rules, 2019 should be referred to. Not withstanding anything contained in these rules, medical management and compensation for injury or death related to biomedical and health research as referred to in Chapter IV of the NDCT Rules, 2019, shall be in accordance with the ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants 2017, from time to time.

7.10.3. Local ECs are responsible for reviewing the relatedness of the SAE to the CHIS and determining the quantum and type of assistance to be provided to the participants, as per the NDCT Rules, 2019. As per SOPs, ECs may set up an SAE subcommittee for causality assessment to thoroughly review reported adverse events. Thus, the EC will be responsible for causality assessment and determining compensation for research-related harm.

7.10.4. Furthermore, section 2.6 of the ICMR National Ethical Guidelines for Biomedical and Health Research involving Human Participants 2017, states that research participants who suffer direct physical, psychological, social, legal or economic harm due to their participation are entitled, after due assessment, to financial or other assistance to compensate them equitably for any temporary or permanent impairment or disability.

7.10.5. The timeline for reporting any AEs must be as per NDCT Rules, 2019 and the ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants 2017

7.10.6. Study expenditure, costs related to ancillary care, medical management and compensation payments should be incorporated into research grants, insurance or corpus funds established by the sponsor, institution or researcher. The study should not be initiated unless planning for the above is in place.

7.10.7. The research study should provide health insurance coverage for all participants during the study and the follow-up period. Insurance may be planned for third parties, such as family members or lab personnel, depending on the nature of the infective organism or where the risk is higher. The provisions for insurance should be made through only India-based companies.

7.11. Follow-up of Participants

7.11.1. Researchers may develop short, medium and long-term plans to follow up as per study requirements. The length of follow-up will vary depending on the nature of the pathogen.

7.11.2. The follow-up should address any adverse effects of the infection, disease progression or treatment related to the study. The duration and plan for the same must be included in the study proposal and be in accordance with the nature of the risks involved.

7.11.3. Participants should be regularly updated with details and information on emerging findings of the research or any other new developments or information that may have potential implications for their health.

7.11.4. Some participants may require long-term psychological support, counselling services or referrals related to stigma, social isolation or psychological distress.

7.12. Post-Study Access/ Benefit Sharing/ Publication

There may or may not be clear and direct benefits to research enrolling for CHIS. However, incase there are any benefits accruing from a study that may have relevance to participating individuals or communities, it is ethically and morally imperative to make those benefits available to the participants.[k]

7.12.1. Participants and participating communities involved in experimental interventions or treatments must be granted access to any direct or indirect benefits that emerge from the study. Some benefits could be shared at the individual level, such as access to counselling services or receiving health care or health education at the site.

7.12.2. Upon completion of the study, the results of the study must be communicated to the participants or communities involved. Both positive as well as negative and inconclusive outcomes must be informed.

[k] During the initial review, the EC should conduct a thorough assessment of the study protocol to ensure the provision of translation of findings or the possibility of affordable access to the product or study outcomes for all participants and their communities after the study.

7.12.3. Recognizing that most interventions evaluated by CHIS have been developed by organizations or companies who own the intellectual property resulting in the intervention, participants should receive prior information regarding any benefits through royalties, patents or commercialization of the drug, treatment or vaccine involved in the intervention.

7.12.4. Local participants and populations must have affordable access to products, drugs and vaccines developed using CHIS in India or through research in international collaboration.

7.12.5. The findings of CHIS must be published and brought out in the public domain, giving due credit and acknowledgment to all participating sites or contributors in a collaborative setting.

8. ETHICS COMMITTEE CONSIDERATIONS

8.1. Structure and Functions of Ethics Committee

The roles and responsibilities of ECs are outlined in the ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants 2017 and there are some additional considerations for ECs reviewing CHIS.

8.1.1. EC may have limited scientific understanding to review studies, involving the creation of a human model and may consider co-opting at least one or two subject experts as independent consultants. These experts would serve as non-voting members for protocol review. The EC may also consider inviting a public representative to provide a lay perspective and to improve the public engagement process.

8.1.2. The EC must assess that the study is well-designed with appropriate methodology, adequate sample size and suitable research sites. Additionally, the study should have obtained approval from the scientific review committee before its submission for ethics review.

8.1.3. The clinical members as well as basic scientists of the EC have the responsibility to ensure a thorough scientific review or primary review. This includes assessing various aspects of the study and the informed consent process. They are required to review the plan for the conduct of the study site, preparation, including clinical laboratory and basic science aspects, follow-up procedures, monitoring, analysis and steps for safeguarding the participants.

8.1.4. Social scientists as well as lay members must carefully look at the socio-cultural dimensions of the study and its implications for individuals, families and communities. Additionally, they need to review the plan for recruitment, informed consent process, plan for isolation and psychological distress involved, if any as well as the potential long-term implications. They may also review built-in provisions for public engagement or plans for building public trust.

8.1.5. The legal expert/s should assess the study's compliance with existing laws, rules, regulations and guidelines. This includes reviewing the availability of insurance schemes, adequacy of provision for payment of compensations in case of injury, other payments and reimbursements, trial agreements, regulatory approvals or permissions, collaborative arrangements and provisions for data sharing and transfer of biological material or data, publications patents and IPR issues.

8.1.6. The EC must be registered with the Department of Health Research (DHR) or Central Drugs Standards and Control Organization (CDSCO) on the Naitik/ Sugam portal, as applicable. The approval letter issued by the EC for the CHIS must bear the registration number and the authority under which it is registered.

8.2. Training of EC

8.2.1. CHIS may often present ethical, legal and regulatory implications. EC members should possess an adequate understanding of the ethico-legal implications of the study. The members must be specifically trained beforehand to improve their understanding of CHIS and updated regarding rules, regulations and guidelines related to CHIS.

8.2.2. For the first few studies, training could be planned with experienced national or international faculty (preferably those experienced in ethical review of CHIS) to equip EC members with knowledge and skills to review CHIS.

8.3. Ethics Review

8.3.1. CHIS should undergo an initial full EC review as per the ICMR National Ethical Guidelines, 2017 at the participating study sites *[See Annexure 3].* The EC secretariat should determine the completeness of submission, including statutory approvals required for conducting the study, Scientific Committee approval, protocol updation based on the recommendations of the scientific committee and the fulfillment of other requirements. Institutions can adapt ICMR Common Forms, which provide a checklist to facilitate submission.

8.3.2. The CHIS proposal must be reviewed in a full committee meeting. EC members should devote time to comprehensively undertake an ethics review, as outlined in the following Table 3.

Table 3 : Framework to guide the ethics review

Review	Factors to be considered
Social Value	• Prospect to add value to public health/ existing policies. • Aid in reducing the burden of diseases/ existing endemic diseases (improved knowledge/ new therapeutics/ vaccine). • Plans for community engagement and building public trust • Community Advisory Board (CAB), if required
Scientific Review	• Appropriate study design and plan for conduct • Careful strain selection, controls and dosing of pathogen • Prior rigorous scientific review done
Benefit and Risk Assessment	• Individual benefit/ benefit to science/ society/ creation of new knowledge • Procedural risks and risk of unexpected symptoms due to exposure of challenge strain • Risks associated with treatment of challenge infection (such as the use of antibiotics) or treatment failure • Additional requirement of isolation/ quarantine and withdrawal restrictions and long-term follow-up • Risks of psychological harm (such as adverse effects of isolation on mental health). Provision for counselling or other mental health support • Risks of social harm (such as stigmatization) and psychosocial support • Risk mitigation plan for third-party infection (research staff/ family/ neighbors/ community) • Planning for any in toward environmental risks (such as leakage of infectionor contamination of effluent water)
Researcher Competence and Experience	• Ethics and GCP training completed • Relevant prior experience in conducting clinical trials • Specific training/ experience to conduct CHIS
Institution	• Reputed tertiary care institution with prior experience of clinical trials • Adequate logistics, trained manpower and infrastructure for CHIS • Isolation facilities and recreational provisions • Budgets to handle any adverse events/ medical management
Participants	• Only healthy adult graduate volunteers • Age between 21-60 years, unless justified • Exclusion of vulnerable populations (children/ pregnant and lactating women/ targeted communities, others)
Consent Process	• Consent form prepared in simple language/ understanding • Time/ space/ counselling/ adequate discussion/ who conducts consent process • Conducting and reviewing Test of understanding • Audio Visual recording • Educational and advocacy material for sensitization • Advertisement /call for volunteers

Protection of Privacy and Confidentiality	• Access of data to restricted study personnel/ regulatory agencies • Confidentiality measures (to avoid stigmatization) • Only necessary and proportionate collection and disclosure of data • Data Sharing plan/ policy
Payments for Participation	• No undue inducement • Reimbursements and payments that are proportionate to the loss of time/ wages/ incidental expenses • Appropriateness of payment amounts in cash/ kind
Conflicts of Interest	• Declaration and management of COI by the researchers, EC members or by the institutional representatives. • Consideration for both financial/ non- financial COI • Decision making to be fair and without biases
Compensation for Research-related Injuries	• Well-defined plan to address CHIS research-related harm for medical management, care, treatment, payment of compensation for research-related injury and ancillary care. • Provisions for Insurance (Indian company only)/ budgetary grants/ provisions under research/ or through corpus funding available at the research institute. • Extended coverage to third parties, if needed
Fair Collaborative Arrangements	• No additional risk in conducting it in India or anywhere else in the world. • Clear and mutual Agreements • Plan for return of research results • No Ethics Dumping in international collaboration • Data sharing/ publications with research participants and in public domain.

8.3.3. In order to address the potential involvement of multiple stakeholders with commercial interests at various levels, the EC should review the study and propose strategies to mitigate conflicts at the level of researchers and institutions. Prior to commencing the review process, the Chairperson must seek a COI declaration from all members, both financial and non-financial and ensure steps for management – for e.g., allowing the individual to leave the room and abstain from decision-making.

8.3.4. EC may review the plan for community engagement, advocacy, and consider various approaches, including the use of social media, to foster public trust. Subsequently, the EC may recommend necessary steps regarding the dissemination of information, public engagement activities and community sensitization. In situations deemed essential, the committee may propose the establishment of a CAB for the study.

8.3.5. EC must ensure that participants are not exposed to unnecessary risks or burdens and that the study is conducted in a manner that minimizes potential harm.

8.3.6. The EC should establish a robust system for monitoring and oversight. It could seek continuing review reports at a desired frequency from researchers based on risk assessment. ECs may also plan to conduct random or for-cause on-site visits and ensure long-term follow-up of study participants.

8.3.7. The EC must review the appropriateness and adequacy of medical care, insurance and, if necessary, extended medical coverage for third parties to address any harm that may occur to participants and/ or third parties. Regular reporting of AE and SAE must be carried out as provided under the NDCT Rules, 2019 and the ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants 2017 as applicable.

8.3.8. If required, the EC may suggest setting up of another sub-committee to closely evaluate SAEs. This SAE sub-committee can consist of two or more members who possess the necessary knowledge and expertise, such as clinicians or experts in clinical pharmacology, to review SAEs in the context of CHIS and advise the EC.

8.3.9. EC must require the establishment of a distinct DSMB to evaluate the progress of the study and conducting interim data analysis. The DSMB is appointed by the study sponsor and is responsible for monitoring the safety, efficacy and well- being of research participants by reviewing the data collected. The DSMB makes recommendations to the study sponsor regarding the continuation, modification, or termination of the trial, based on the data collected. Based on the insights provided by the DSMB, the study may be prolonged, modified, or ceased accordingly. DSMB reports, whenever available, must be shared with the EC by the investigators for necessary consideration.

8.3.10. In the case of the use of organism/ recombinant/ bioengineered CHIS agent, an Institutional Biosafety Committee (IBSC) must review the study in compliance with the Regulations and Guidelines on Biosafety of Recombinant DNA Research & Biocontainment, 2017 and the Handbook for Institutional Biosafety Committee, 2020 along with other relevant guidelines issued by the Department of Biotechnology time to time, and as required under the Rules for the Manufacture, Use, Import, Export and Storage of Hazardous Microorganisms/ Genetically Engineering Organisms or Cells, 1989 notified under the Environment (Protection) Act, 1986.

8.3.11. If a challenge strain is imported, it is essential to submit all related documents and validation certificates for review by the EC. This ensures transparency and verifies that the imported strain adheres to necessary standards and safety protocols before it is used in the study. [l]

8.3.12. In case a common review is planned for multicentric CHIS, a comprehensive common review may be conducted. In such cases, the designated EC may undertake a full review and share its recommendations. The local ECs at participating sites can decide to accept or undergo its own review. They can focus on site-specific requirements, assess institutional readiness to conduct the research, monitor the informed consent process and address any other local concerns. Participating site ECs should establish effective communication among sites to ensure a timely and efficient ethics review for research. For regulatory clinical trials, all requirements specified under NDCT Rules, 2019 or other applicable regulations should be followed.

9. ADVOCACY, PUBLIC ENGAGEMENT AND PUBLIC TRUST

In view of the limited understanding of CHIS amongst the public, researchers have an obligation to initiate steps to engage with the public and undertake trust-building exercises. This involves committing time and resources, educating research group, listening to concerns, clarifying the public's understanding, addressing misconceptions and providing information in a timely manner to improve understanding. Researchers also need to acknowledge the public's input on the social value of the study and disseminate correct information in a timely manner.

9.1. Researchers should adopt different modes of public engagement *[See Annexure 4]*, depending on the public perception of the risk involved and alleviate fear or any misinformation among the public and media. Prior social science research may be conducted to understand social acceptability, study payment, benefits and burdens.

[l] Importing strain is a regulatory step and relevant permissions are required for conducting the study.

9.2. Persons from the media (print, electronic, social), various public/ stakeholders (potential study participants, researchers, EC members and so on), professionals, leaders, NGOs working with communities, representatives, government officials, legal community, religious leaders, philosophers and other should be invited to consultation meetings to promote public understanding and acceptance of CHIS through education and engagement with representatives. The research team should actively initiate dialogues/ interaction with the public from which the participants are drawn. Efforts should be made to resolve differences of opinion with representatives/ stakeholders through respectful approaches.

9.3. Providing clear and concise information to media and ensuring accurate, responsible and balanced reporting of CHIS enhances public trust. Researchers should disseminate information through media about the study's objective and invite feedback from public through in-person interactions, mail, electronic channels and social media platforms following approval of the proposal by the EC. Additionally, audio-visual aids may be employed to facilitate a better public understanding of the study.

9.4. Open interviews to capture participants' experiences should be conducted to ensure trust and transparency in a respectful and informative manner. These experiences may be shared on public platforms while maintaining anonymity, privacy and confidentiality.

9.5. Researchers as well as ethics committees may consider encouraging mechanisms to receive and address doubts, queries and complaints, preferably through an email, website, webpage, or blog created specifically for the CHIS.

10. RESEARCH GOVERNANCE

The existing guidance or regulatory frameworks, as applicable to biomedical and health research or a clinical trial need to be followed depending on the type of CHIS under consideration.

10.1. The Drugs and Cosmetics Act, 1940 read with NDCT Rules, 2019 governs the conduct of clinical trials as well as biomedical and health research. The Rules contain detailed provisions related to regulatory approvals, ethics review and the safeguarding of participant protection and safety.

10.2. Moreover, Rule 16(4) of the NDCT Rules, 2019 mandates that all research must strictly adhere to the ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017. Consequently, researchers bear a legal responsibility to ensure that their work aligns with these guidelines in addition to complying with the relevant provisions within the NDCT Rules, 2019.

10.3. CHIS models used in regulatory clinical trials for drugs, vaccines and medical devices must obtain approval from the CDSCO. Furthermore, researchers may be answerable if a regulatory authority is appointed by the Government of India (GOI) for these studies.[m]

10.4. Compliance with current Good Manufacturing Practices (cGMP) for the use of challenge strain and as required under the NDCT Rules, 2019. This includes registration of the study on the Clinical Trials Registry-India.

10.5. Laboratories participating in CHIS should have compliance with GLP as prescribed by the Organization for Economic Cooperation and Development (OECD). These laboratories should receive accreditation from the National Accreditation Board for Testing and Calibration Laboratories (NABL).

10.6. EC should be registered with regulatory authorities, such as CDSCO and/ or DHR, as per NDCT Rules, 2019.

10.7. All regulatory approvals needed for the conduct of the CHIS in question need to be obtained and copies of such approvals are to be forwarded by the investigator to the CDSCO.

10.8. For genetically modified strains, under Rules for the Manufacture, Use, Import, Export and Storage of Hazardous Microorganisms/ Genetically Engineering Organisms or Cells, 1989, notified under the Environment (Protection) Act, 1986, permission from the Review Committee on Genetic Manipulation (RCGM) and the Genetic Engineering Appraisal Committee (GEAC), as applicable, is required. Additionally, compliance with the Regulations and Guidelines for Recombinant DNA Research and Biocontainment, 2017, is necessary to the extent that they are applicable to the research with challenge strain.

[m] ICMR is willing to review the first five CHIS proposals submitted by institutions intending to conduct CHIS in the country, with the aim of fostering public trust and upholding the highest ethical standards.

10.9. The certification of the laboratory's biosafety level, as mandated by the Guidelines for establishing Containment Facilities, must be determined on a case-by-case basis to ensure appropriate biosafety measures are in place.

10.10. The Institute planning the CHIS should constitute an IBSC to deal with genetically engineered and non-genetically engineered hazardous microorganisms, as applicable.

10.11. In the case of international collaboration or funding, registration may be required from with BioRRAP along with approval from the Health Ministry's Screening Committee (HMSC) as applicable.

LIST OF REFERENCES

1. A framework for Controlled Human Infection Model (CHIM) studies in Malawi: Report of a Wellcome Trust workshop on CHIM in Low-Income Countries held in Blantyre, Malawi. Wellcome Open (Accessed 24 Aug 2023).

2. Association for the Accreditation of Human Research Protection Programmes (AAHRPP). Available from: ***https://www.aahrpp.org/*** (Accessed 13 Oct 2023).

3. Biological Research Regulatory Approval Portal (BioRRAP) Available from: ***https://biorrap.gov.in/*** (Accessed 09 Oct 2023).

4. Central Drug Standards and Control Organization (CDSCO) SUGAM online portal. Available from: ***https://www.cdscoonline.gov.in/CDSCO/homepage*** (Accessed 03 Jul 2023).

5. Clinical Trials Registry – India. Available from: ***http://www.ctri.nic.in*** (Accessed 09 Oct 2023).

6. Code of Medical Ethics Regulations. National Medical Commission. 2002. Available from: ***https://www.nmc.org.in/rules-regulations/code-of-medical-ethics-regulations-2002/#:~:-text=He%20shall%20keep%20himself%20pure,the%20actions%20of%20his%20life.*** (Accessed 08 Nov 2023)

7. Common Forms for Ethics Committee Review. Available from: ***https://ethics.ncdirindia.org/Common_forms_for_Ethics_Committee.aspx***

8. Considerations on the principles of development and manufacturing qualities of challenge agents for use in human infection models: Wellcome Trust; 2022. Available from: ***[https:// 42armoni.figshare.com/ndownloader/files/34591550].*** (Accessed 10 Oct 2023).

9. Controlled Human Infection Model Studies Summary of a workshop held on 6 February 2018. The Academy of Medical Sciences. Available from: ***https:/acmedsci.ac.uk/file-download/55062331*** (Accessed 12 Oct 2023).

10. Controlled Human Infection Studies in the Netherlands – ROADMAP. ZonMw. 2023. Available from: ***https://www.zonmw.nl/sites/zonmw/files/2023-05/Controlled-Human-Infection-Studies-in-the-Netherlands_Roadmap.pdf*** (Accessed 09 Oct 2023).

11. Ethics dumping: Case studies from North-South Research Collaborations. Cham, Switzerland: Springer Open; 2018.

12. Fourth Controlled Human Infection Model (CHIM) Meeting – CHIMs in endemic countries, May 22-23, 2023. (Unpublished).

13. Good Clinical Practice. New Delhi: Central Drugs Standard Control Organization; 2004. Available from: ***https://rgcb.res.in/documents/Good-Clinical-Practice-Guideline.pdf*** (Accessed 03 Oct 2023).

14. Good Laboratory Practice (GLP) – The OECD Principles of Good Laboratory Practice (GLP). Available from: *https://www.oecd.org/chemicalsafety/testing/good-laboratory-practiceglp.htm* (Accessed 09 Oct 2023).

15. Good manufacturing practice (GMP) resources. 2019. Available from: *https://ispe.org/initiatives/regulatory-resources gmp* (Accessed 09 Oct 2023).

16. Guidelines and Handbook for Institutional Biosafety Committees (IBSCs); 2011. Available from: *https://ibkp.dbtindia.gov.in/Content/FlashPDF/IBSC%20Handbook.pdf* (Accessed 03 Oct 2023).

17. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6 (R2) ;2016. Available from: *https: //database.ich.org /sites /default /files /E6_R2_Addendum.pdf* (Accessed 03 Oct 2023)

18. Key criteria for the ethical acceptability of COVID-19 Human Challenge Studies. World Health Organization; 2020. Available from: *https://www.who.int/publications/i/item/WHO-2019-nCoV-Ethics_criteria-2020.1* (Accessed 04 Oct 2023).

19. Naitik Portal for National Ethics Committee Registry for Biomedical and Health Research (NECRBHR) under the Department of Health Research. Available from: *https://naitik.gov.in/DHR/Homepage* (Accessed 03 Oct 2023).

20. National Accreditation Board for Hospitals and Healthcare Providers (NABH).Accreditation Standards for Ethics Committees. 1 st ed. 2016. Available from: *https://nabh.co/ClinicalTrial.aspx#gsc.tab=0* (Accessed 13 Oct 2023).

21. National Accreditation Board for Testing and Calibration Laboratories. Available from: *https://nablwp.qci.org.in/Home/index* (Accessed 09 Oct 2023).

22. National Ethical Guidelines for Biomedical and Health Research involving Human Participants. New Delhi: Indian Council of Medical Research;2017. Available from: *https://ethics.ncdirindia.org/asset/pdf/ICMR_National_Ethical_Guidelines.pdf* (Accessed 03 Oct 2023).

23. New Drugs and Clinical Trials Rules, 2019. Available from: *https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf.*

24. Regulations&GuidelinesforRecombinantDNAResearchandBiocontainment;2017.Available from:*https://ibkp.dbtindia.gov.in/DBT_Content_TestCMSGuidelines/20181115134719867_Regulations-Guidelines-for-Reocminant-DNA-Research-and-Biocontainment-2017.pdf* (Accessed 03 Oct 2023)

25. Report: "The Ethics of controlled human infection model studies for mitigating pandemic risks". 2023. Available from: *https://www.practicalethics.ox.ac.uk/article/report-the-ethics-of-controlled-human-infection-model-studies-for-mitigating-pandemic-risks* (Accessed 09 Oct 2023).

26. Revised Simplified Procedure/ Guidelines on Import, Export, and Exchange of GE organisms. Report no.: BT/BS/17/635/2015-PID.Department of Biotechnology; 2020 Jan 17. Available from: *https://ibkp.dbtindia.gov.in/PageContent/ShowBrowsedFile?FileName=20200423124040845_Revised%20simplified%20procedure%20guidelines.pdf&FPath=E:%5C%5CDBT_Content_Test%5CCMS%5CGuidelines/20200423124040845_Revised%20simplified%20procedure%20guidelines.pdf* (Accessed 02 Nov 2023).

27. Side Meeting on the Current Global Regulatory and Ethical Landscape for CHIM Studies including Regional/Global Collaborative Guidance. Available from: *https://media.tghn.org/articles/Side_Meeting_on_the_Current_Global_Regulatory_and_Ethical_Landscape_for_CHIM_Studies.pdf* (Accessed 05 Oct 2023).

28. Strategic Initiative for Developing Capacity in Ethical Review – Foundation for Promoting the Development of Human Research Ethics (SIDCER-FERCAP). Available from: *https://www.sidcer-fercap.org/pages/home.html* (Accessed 13 October 2023).

29. Use of human infection studies in vaccine development. Wellcome Trust; 2023. Available from: *https://figshare.com/articles/online_resource/Use_of_Human_Infection_Studies_in_Vaccine_Development/21997619* (Accessed 12 Oct 2023).

30. WHO Expert Committee on Biological Standardization. Sixty-seventh report. Annex 10. Human challenge trials for vaccine development: regulatory considerations. World Health Organization. Available from: *https://cdn.who.int/media/docs/default-source/biologicals/who_trs_1004_web_annex_10.pdf?sfvrsn=16a191da_5&download=true.* (Accessed 11 Oct 2023).

31. WHO guidance on the ethical conduct of controlled human infection studies. Geneva World Health Organization; 2021. Available from: *https://www.who.int/publications/i/item/9789240037816* (Accessed 03 Oct 2023).

SUGGESTED FURTHER READING

1. Adams-Phipps J, Toomey D. Standardizing controlled human infection study reporting discussion and guidelines. Authorea (Authorea) [Internet]. 2023 Mar 3; Available from: *https://doi.org/10.22541/au.167785775.55591277/v1*

2. Baay M, Neels P. SARS-CoV-2 controlled human infection models: Ethics, challenge agent production and regulatory issues. Biologicals [Internet]. 2020 Sep 1;67:69–74. Available from: *https://doi.org/10.1016/j.biologicals.2020.08.006*

3. Balasingam S, Horby P, Wilder-Smith A. The potential for a controlled human infection platform in Singapore. Singapore Medical Journal [Internet]. 2014 Sep 1;55(09):456–61. Available from: *https://doi.org/10.11622/smedj.2014114*

4. Bambery B, Selgelid MJ, Weijer C, Savulescu J, Pollard AJ. Ethical Criteria for Human Challenge Studies in Infectious Diseases: Table 1. Public Health Ethics [Internet]. 2015 Sep 27;9(1):92–103. Available from: *https://doi.org/10.1093/phe/phv026*

5. Bekeredjian Ding I, Trouvin J, Depraetere H, La C, Suvarnapunya AE, Bell AS, et al. Controlled Human Infection Studies: Proposals for guidance on how to design, develop and produce a challenge strain. Biologicals [Internet]. 2021 Nov 1;74:16–23. Available from: *https://doi.org/10.1016/j.biologicals.2021.09.002*

6. Binik A. What risks should be permissible in controlled human infection model studies? Bioethics [Internet]. 2020 Mar 1;34(4):420–30. Available from: *https://doi.org/10.1111/bioe.12736*

7. Bompart F, Fisher JA, Allen E, Sevene E, Kumar N, Chew CK, et al. The VolREthics initiative to protect the well-being of healthy volunteers in biomedical research. Nature Medicine [Internet]. 2023 Aug 14;29(10):2393–4. Available from: *https://doi.org/10.1038/s41591-023-02490-6*

8. Deming ME, Michael NL, Robb ML, Cohen MS, Neuzil KM. Accelerating development of SARS-COV-2 vaccines — The role for controlled human infection models. The New England Journal of Medicine [Internet]. 2020 Sep 3;383(10):e63. Available from: *https://doi.org/10.1056/nejmp2020076*

9. Dholakia S. Conducting controlled human infection model studies in India is an ethical obligation. Indian Journal of Medical Ethics [Internet]. 2018 Oct 13;III(4):279–85. Available from: *https://doi.org/10.20529/ijme.2018.083*

10. Eberts JD, Zimmer-Harwood P, Elsey JWB, Fraser-Urquhart A, Smiley T. Volunteering for Infection: Participant Perspectives on a hepatitis C virus controlled Human infection model. Clinical Infectious Diseases [Internet]. 2023 Aug 14;77(Supplement_3):S224–30. Available from: *https://doi.org/10.1093/cid/ciad350=*

11. Egesa M, Ssali A, Tumwesige E, Kizza M, Driciru E, Luboga F, et al. Ethical and practical considerations arising from community consultation on implementing controlled human infection studies using Schistosoma mansoni in Uganda. Global Bioethics [Internet]. 2022 Jul 4;33(1):78–102. Available from: *https://doi.org/10.1080/11287462.2022.2091503*

12. Lynch HF. The right to withdraw from controlled human infection studies: Justifications and avoidance. Bioethics [Internet]. 2020 Jan 24;34(8):833–48. Available from*: https://doi.org/10.1111/bioe.12704*

13. Gbesemete D, Barker M, Lawrence W, Watson D, De Graaf H, Read RC. Exploring the acceptability of controlled human infection with SARSCoV2—a public consultation. BMC Medicine [Internet]. 2020 Jul 7;18(1). Available from: *https://doi.org/10.1186/s12916-020-01670-2*

14. Gopichandran V, Kang G. Theme Editorial: Controlled Human Infection Models: Exploring the landscape in India. Indian Journal of Medical Ethics [Internet]. 2018 Oct 13;III(4):270–3. Available from: *https://doi.org/10.20529/ijme.2018.082*

15. Grimwade O, Savulescu J, Giubilini A, Oakley J, Osowicki J, Pollard AJ, et al. Payment in challenge studies: ethics, attitudes and a new payment for risk model. Journal of Medical Ethics [Internet]. 2020 Sep 25;46(12):815–26. Available from: *https://doi.org/10.1136/medethics-2020-106438*

16. Jain A. Controlled human infection models: Promises and concerns for India [Internet]. IndiaBioscience. 2020. Available from: *https://indiabioscience.org/columns/indian-scenario/controlled-human-infection-models-promises-and-concerns-for-india*

17. Jamrozik E, Selgelid MJ. Human infection challenge studies in endemic settings and/or low-income and middle-income countries: key points of ethical consensus and controversy. Journal of Medical Ethics [Internet]. 2020 May 7;46(9):601–9. Available from: *https://doi.org/10.1136/medethics-2019-106001*

18. Kirchhelle C, Vanderslott S. Editorial: The Need for Harmonised International Guidelines ahead of COVID-19 Human Infection Studies. Public Health Reviews [Internet]. 2021 Jan 29;42. Available from: *https://doi.org/10.3389/phrs.2021.1603962*

19. Morrison H, Jackson SE, McShane H. Controlled human infection models in COVID-19 and tuberculosis: current progress and future challenges. Frontiers in Immunology [Internet]. 2023 May 25;14. Available from: *https://doi.org/10.3389/fimmu.2023.1211388*

20. Rapeport G, Smith E, Gilbert A, Catchpole A, McShane H, Chiu C. SARS-CoV-2 Human Challenge Studies — Establishing the Model during an Evolving Pandemic. The New England Journal of Medicine [Internet]. 2021 Sep 9;385(11):961–4. Available from: *https://doi.org/10.1056/nejmp2106970*

21. Roestenberg M, Hoogerwerf MA, Ferreira DM, Mordmüller B, Yazdanbakhsh M. Experimental infection of human volunteers. Lancet Infectious Diseases [Internet]. 2018 Oct 1;18(10):e312–22. Available from: *https://doi.org/10.1016/s1473-3099(18)30177-4*

22. Roestenberg M, Mordmüller B, Ockenhouse C, Mo AX, Yazdanbakhsh M, Kremsner PG. The frontline of controlled human malaria infections: A report from the controlled human infection models Workshop in Leiden University Medical Centre 5 May 2016. Vaccine [Internet]. 2017 Dec 1;35(51):7065–9. Available from: *https://doi.org/10.1016/j.vaccine.2017.10.093*

23. Rose A, Sekhar A. Bioethics of establishing a CHIM model for dengue vaccine development. International Journal of Infectious Diseases [Internet]. 2019 Jul 1;84:S74–9. Available from: *https://doi.org/10.1016/j.ijid.2019.01.013*

24. Rose A. The ethics of volunteer selection and compensation in Controlled Human Infection Models in India. Indian Journal of Medical Ethics [Internet]. 2018 Oct 13;III(4):285–9. Available from: *https://doi.org/10.20529/ijme.2018.084*

25. Sekhar A, Kang G. Human challenge trials in vaccine development. Seminars in Immunology [Internet]. 2020 Aug 1;50:101429. Available from: *https://doi.org/10.1016/j.smim.2020.101429*

26. Selgelid MJ, Jamrozik E. Ethical challenges posed by human infection challenge studies in endemic settings. Indian Journal of Medical Ethics [Internet]. 2018 Oct 13;III(4):274–8. Available from: *https://doi.org/10.20529/ijme.2018.073*

27. Shah SK, Miller FG, Darton TC, Duenas DM, Emerson C, Lynch HF, et al. Ethics of controlled human infection to address COVID-19. Science [Internet]. 2020 May 22;368(6493):832–4. Available from: *https://doi.org/10.1126/science.abc1076*

28. Sharma A, Apte A, Rajappa M, Vaz M, Vaswani V, Goenka S, et al. Perceptions about controlled human infection model (CHIM) studies among members of ethics committees of Indian medical institutions: A qualitative exploration. Wellcome Open Research [Internet]. 2023 Feb 28;7:209. Available from: *https://doi.org/10.12688/wellcomeopenres.17968.2*

29. Stunkel L, Grady C. More than the money: A review of the literature examining healthy volunteer motivations. Contemporary Clinical Trials [Internet]. 2011 May 1;32(3):342–52. Available from: *https://doi.org/10.1016/j.cct.2010.12.003*

30. Timms O. Protecting challenge study participants in low and middle income settings. Indian Journal of Medical Ethics [Internet]. 2018 Oct 13;III(4):289–92. Available from: *https://doi.org/10.20529/ijme.2018.085*

31. Vaswani V, Saxena A, Shah SK, Palácios R, Rid A. Informed consent for controlled human infection studies in low and middle income countries: Ethical challenges and proposed solutions. Bioethics [Internet]. 2020 Aug 10;34(8):809–18. Available from: *https://doi.org/10.1111/bioe.12795*

32. Vaz M, Timms O, Johnson AR, S RK, Ramanathan M. Public perceptions on Controlled Human Infection Model (CHIM) studies—a qualitative pilot study from South India. Monash Bioethics Review [Internet]. 2020 Oct 21;39(1):68–93. Available from: *https://doi.org/10.1007/s40592-020-00121-1*

33. 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 Journal of Medical Ethics [Internet]. 2019 Jun 14;01–5. Available from: *https://doi.org/10.20529/ijme.2019.030*

34. Vaz M. Public engagement in the context of a CHIM study. Indian Journal of Medical Ethics [Internet]. 2018 Oct 13;III(4):296–300. Available from: *https://doi.org/10.20529/ijme.2018.087*

ANNEXURES

Annexure 1a – Informed Consent

Definition:

The process of full disclosure of the nature of the research and the participant's involvement ensures adequate comprehension associated with the particular study/ intervention through which participants provide their voluntary choices/ agreement to participate

Introduction:

Seeking valid consent from CHIS participants through contextualized consent procedures is an ethical requirement because participants may not fully understand the potential risks and obligations of the participants and maybe subjected to undue inducements or coercion.

Purpose:

To ensure that participants are fully informed and possess a clear understanding of the study's purpose, procedures, anticipated risks and benefits and the opportunity for the participant to ask any questions at any time during the study.

Aims:

- To provide relevant information to potential participants.
- To let the participant have the freedom of making choices to participate or withdraw from the study and assure voluntariness.
- To ensure that the participant can make an informed decision.
- To ensure the information is easily comprehended by the participants.

Steps:

- Ensure participant comprehend and understand the information.
- Encourage participants to ask questions. Allow them to consult with family doctors, relatives and community members.
- Provide sufficient information to the participant in a language that they can understand.
- Ensure altruistic and voluntary participation.

Additional considerations for CHIS:

Refer Table 2 for additional consideration for the conduct of CHIS

Informed Consent Process:

- Selecting of the right individuals to participate in CHIS, preferably literate participants from middle and upper socio-economic strata of the society.
- Conducting detailed one-to-one interaction with the participants and providing opportunity for discussions with their immediate families (where relevant).
- Providing information on payment for participation and compensation for research-related injuries.
- Providing an opportunity for the participants to discuss with family and friends before they consent.
- Detailing the need for long-term follow-up if required.
- Educating participants about the risk of third-party transmission and infection control measures upon withdrawal from the research.
- Administering a test of understanding to evaluate whether the participants have fully understood the study.
- Recording the informed consenting process through audio-visual means.
- Arranging visits to the on-site facility and an orientation to the facilities for the participants.

Withdrawal:

- The ethical right of participants to withdraw from CHIS may result in harm to the participant, inadvertent disease transmission and detrimental impacts to third parties in close contact with the study volunteer.
- The participant should receive full information about the consequence of withdrawal from the study, or extra precautions that may be required if premature withdrawal is unavoidable.
- The participant should be made aware that in case of withdrawal, whether voluntary or at the investigator's discretion, the participant may have to undergo confinement for a quarantine period.
- The consent process should highlight this difference in withdrawal from CHIS compared to other clinical trials, emphasizing the potential need for participant to undergo confinement for a quarantine period in case of withdrawal. Also, it may be mentioned that withdrawal may not be possible if the study has reached a certain stage.

Outcome:

- Enrolling participants who are fully informed about the study.
- Ensuring that participant autonomy is protected while enrolling them in a study that involves the injection of an agent which has a potential to harm.

*Annexure 1b – Essential Information for Consenting

Before requesting consent to participate in controlled human infection studies (CHIS), information addressing the following aspects of the study should be provided to potential participants. in clear, concise and accessible language and opportunities to discuss specific aspects and address queries must be provided. Individual jurisdictions may have additional specific informational requirements.

1. WHY THE RESEARCH IS BEING DONE:
   - Pathogen and associated health burdens (locally and globally)
   - Research questions
   - Anticipated social and scientific value
2. ELIGIBILITY CRITERIA
3. EXCLUSION CRITERIA
4. NUMBER OF PARTICIPANTS IN THE STUDY
5. WHAT WILL HAPPEN DURING THE STUDY (PROCEDURE, TIME(S)/FREQUENCY, DURATION, LOCATION)
   - Screening process
     - Feedback of results
     - Potential public health reporting requirements [where relevant]
   - Research procedures
     - Infection or disease model
     - Exposure to infection
       - Mode and dosage
       - Differing research arms/ groups [where relevant]
     - Experimental treatments/ vaccines
       - Differing research arms/ groups [where relevant]
     - Monitoring and diagnosis
     - Treatment [where relevant]
   - Infection control measures and compliance requirements [where relevant]
   - Post-trial monitoring [where relevant]
6. ADDITIONAL BURDENS:
   - Time commitments
   - Symptoms of infection/ disease [where relevant]
7. RISKS (COMMON AND RARE, DURING AND SUBSEQUENT TO RESEARCH):
   - Risks of exposure to the micro-organism strain
   - Risks of exposure to experimental vaccines and/ or treatments [where relevant]
   - Risks associated with diagnostic measures (for example, frequent blood draws)
   - Risks of psychological and/ or social harm
   - Potential for additional unknown risks
8. POTENTIAL PERSONAL BENEFITS, IF ANY
9. PROPOSED FEEDBACK OF INDIVIDUAL RESULTS FROM SCREENING AND DIAGNOSTIC TESTS
10. VOLUNTARINESS OF PARTICIPATION
11. OPTION TO WITHDRAW
    - Nature of ongoing obligations to comply with measures for participant safety and/ or infection control measures following withdrawal and avenues for appeal [where relevant]

12. REASONS PARTICIPANTS MAY NEED TO BE WITHDRAWN FROM THE STUDY BY RESEARCHERS
13. ALTERNATIVES TO PARTICIPATION [IF RELEVANT]
14. PARTICIPANT RESPONSIBILITIES • Disclosure of relevant information prior to research • Avoidance of actions which may adversely affect participants or study results • Feedback to research team needed to enable effecting monitoring and risk/ burden minimization (reporting onset of disease symptoms, for example) [where relevant] • Infection control [where relevant] – Compliance – Discussion about infection control measures with relevant third parties
15. PERSONAL PRIVACY • Protection of privacy during research • Protection of identifiable private information – Limits (public health reporting requirements, for example) [where relevant]
16. SAMPLES AND DATA • Data confidentiality and protections – Limits (public health reporting requirements, for example) [where relevant] • Uses in current study • Potential storage and future uses • Sharing • Genetic testing / sequencing [where relevant]
17. REQUEST TO ACCESS PARTICIPANTS' HEALTH RECORDS [WHERE RELEVANT] • Which information • Proposed uses • Who will have access?
18. REIMBURSEMENT FOR OUT-OF-POCKET COSTS
19. COMPENSATION FOR PARTICIPATION (FINANCIAL AND NON-FINANCIAL) • Itemized by study process/ stage • Incentive/ bonus [where relevant] • Timing and methods of compensation
20. TREATMENT AND COMPENSATION FOR RESEARCH-RELATED HARMS
21. ETHICAL REVIEW AND APPROVAL, CONTACT DETAILS
22. OPPORTUNITY TO DISCUSS QUERIES WITH THE RESEARCH TEAM • Prior to consent • During research
23. CONTACT FOR CONCERNS OR RESEARCH-RELATED HARMS
24. RESEARCHERS' RESPONSIBILITY TO INFORM PARTICIPANTS ABOUT: • Novel research findings which may influence study design or participants' decisions to take part in research, and the potential to seek revised consent [where relevant] • Protocol violations and implications
25. PROPOSALS TO ASSESS PARTICIPANT UNDERSTANDING [WHERE RELEVANT].

**Annexure 1b is reproduced from "WHO guidance on the ethical conduct of controlled human infection studies". Geneva: World Health Organization; 2021 with permission*

Annexure 2 – Test of Understanding

Definition:

A simple oral or written test designed to provide assurance that participants have the capacity to consent and understand what study participation will require of them, including the risks of deliberate infection.

Introduction:

Informed consent is a critical component of biomedical health research, yet participants' comprehension of the information offered is frequently inadequate. During the consenting procedure, it is necessary to test the level of understanding of the prospective study participants to check whether they all are well comprehended about the study.

Purpose:

To ensure that the participants understood the necessary information about the study to make an informed decision about participation in the research being conducted.

Aims:

- To assess capacity for giving informed consent for the study.
- To confirm voluntary participation.

Ways of Testing:

- Engage in extended discussions with the participant, encouraging them to inquire about the study.
- The participant must be able to describe the study, associated risks and expected requirements for participation.
- Utilize test quizzes to evaluate the participant's understanding. The questions must be framed in a way that assesses the participant's understanding of the method of study, intentional harm, expectations from the participants, withdrawal procedures, risk of third-party infection, the possibility of isolation etc.
- Design open-ended questions or tests to help improve the process, providing participants with an opportunity to express information based on their understanding.

Test of understanding with examples of open-ended questions

1. Study Purpose and Procedures

1.1. Please describe, in your own words, the purpose of this research.

1.2. Can you explain the main procedures involved in this study and what will be expected from you as a participant

2. Informed Consent

2.1. What is informed consent, and why is it essential for your participation in this study?

2.2. What are your rights as a research participant and how does informed consent protect you?

3. Risks and Benefits

3.1. Identify and describe some potential risks associated with participating in this study.

3.2. What are the potential benefits that you and others may gain from your participation in this study?

4. Withdrawal and Disqualification

4.1. If you decide to withdraw from the study, what options do you have and what are the potential consequences of withdrawal?

4.2. Under what circumstances could you be disqualified from the study and what would be the reasons for such disqualification?

5. Confidentiality and Privacy 5.1. How will your personal information and data be handled to ensure confidentiality during the study? 5.2. Can you describe the measures the research team will take to protect your privacy throughout the study? 6. Safety and Medical Support 6.1. What precautions are in place to ensure your safety during the study? 6.2. How will you contact us or report any adverse effects? 7. Payment and Compensation for research-related injuries 7.1. Why do you think you will receive a payment to join this research? 7.2. If you suffer from an injury who will pay and how? 8. Voluntary Participation 8.1. Is your participation in this study voluntary and if so, what does that mean? 8.2. Under what circumstances you could be forced to participate against your will?
Primary Outcome: • Quantitative rates of participant understanding/ knowledge and decision-making capacity. • Getting a fully informed study participant.
Secondary Outcome: • Participant retention, satisfaction, and accrual.

*Annexure 3 – Checklist for Ethics Committee

Issues to address during the ethical review of CHIS include:

1. JUSTIFICATION – DOES THE STUDY HAVE APPROPRIATE, SUFFICIENT AND SCIENTIFIC VALUE?
   - What is the research question?
     - Is the research question important?
     - Does the study have the capacity to provide valuable new information to address the research question?
   - Will the results of the study contribute to:
     - Understanding the infection and/ or
     - Prevention and/ or treatment or the infection and/ or
     - A programme of research focused on understanding the infection and contributing to its prevention and/ or treatment?
   - Are the results of the study anticipated to be generalizable to the relevant population?
     - If not, is the use of a model of infection that will not produce generalizable results justified?
   - If a placebo arm is planned:
     - Is there scientific confirmation that a placebo arm is needed?
     - What are the consequences of being on the placebo arm and how will these be appropriately managed?
     - Has post-trial access to treatment for the placebo group been considered?
   - Will conducting the study detract from clinical care/ public health responses to the infection?
   - Are there equally feasible alternative research methods which are likely to provide similarly meaningful answers equally rapidly?

2. RESEARCH DESIGN
   - What has informed the study design?
   - Has there been consideration of the role of consultation and engagement with expert stakeholders, communities and publics to inform the design and conduct of the research?
   - Has there been independent expert scientific peer review of the proposal?
   - Has there been a systematic review of relevant literature?
     - Will relevant literature be monitored throughout the research, and amendments to the protocol proposed where appropriate?
   - Has the choice of the micro-organism strain and model of infection been explained and justified?
   - Are researchers proposing to use the best approach to diagnose the infection and/ or provide the best treatment as early as possible?
     - If not, what additional risks and burdens are associated with the proposed approach?
     - Are any additional risks and burdens justified?
   - Does the research design effectively address infection control requirements?
   - Will infection control measures have implications for participants who wish to withdraw from the research?

3. RISKS, BURDENS AND BENEFITS

- Have the physical, psychological and social risks and burdens been identified, minimized, and assessed accurately enough to be evaluated?
- What uncertainties are associated with research risks?
- Will the potential benefits of the proposed study outweigh the risks and burdens?
- Are the risks and burdens individually and cumulatively acceptable?
- Are there any potential benefits associated with research participation?
- How will participant risks and burdens be managed and minimized during and following the research?
- How will treatment and compensation be provided for any research-related injuries sustained during or subsequent to the research?
- How will risks to third parties be managed and minimized?
- Is the quality of the micro-organism strain assured?
  - What manufacturing standards have been used?
  - Has evidence of quality control been provided?
- How will micro-organism strains be safely and securely transferred, stored, used and disposed of?

4. SITE SELECTION

- Does the research address health priorities in the target population?
- Does the research team have appropriate relevant expertise to conduct the research and is there appropriate clinical expertise to treat any resulting infection/disease?
- Does the research site have the appropriate infrastructure, facilities, personnel and processes to effectively and safely conduct the research?
- Has there been consultation with local key stakeholders about the safe and effective conduct of the research and whether it is acceptable?

5. PARTICIPANT SELECTION

- What are the proposed inclusion and exclusion criteria and what considerations (including risk minimization for participants and third parties) have informed their development?
- Will participants with diminished capacity to consent, or incompetent participants, be eligible to participate?
  - If so, what additional processes and protections will be implemented?
- How will potential participants be approached?
- What screening processes will be implemented for potential participants:
  - to promote scientific validity and/or
  - to minimize potential risks and burdens?

6. CONSENT AND NOTIFICATION

6a Consent

- Do the research staff involved in consent processes have the appropriate training, expertise, experience and accountability frameworks?
- Is the design and development of consent processes and documentation informed by:
  - A review of literature including:
    - Relevant evidence-based approaches to the effective design and conduct of consent processes?
    - Relevant social science research into CHIS?

– Consultation and engagement with
  - Communities and public?
  - Key stakeholders?
- Are the proposed consent process and associated materials appropriate?
- What opportunities will there be for participants to reflect, discuss with others, and ask questions?
- What key aspects of the research must the participants understand?
  – How will their understanding of these be promoted and evaluated?

6b. Notification
- Does the research pose acceptable risks to third parties which require notification?
  – If so, how will third parties be notified about potential risks?

7. REIMBURSEMENT, COMPENSATION AND INCENTIVES
- Has a schedule and breakdown of proposed approaches to reimbursement and compensation been provided? Is this appropriate?
- How will participants be reimbursed for out-of-pocket expenses?
- Will participants be compensated for research participation?
- Are there proposals to offer additional incentives to participate?

8. PRIVACY AND CONFIDENTIALITY
- How will participants' privacy be protected?
  –Are there conditions under which identifiable details about participants may be shared with third parties, such as public health authorities?

9. DATA MANAGEMENT AND SHARING
- How will research data be curated, securely stored, and shared?
- How will research methods, materials and findings be shared?

10. REVIEW AND OVERSIGHT
- Is there a trial steering committee in place?
- Is a data safety and monitoring committee in place?
- Will the study protocol be registered and published?
- How will safety reports of adverse events and serious adverse events be shared?

**Annexure 3 is reproduced from "WHO guidance on the ethical conduct of controlled human infection studies". Geneva: World Health Organization; 2021 with permission*

Annexure 4 – Public Engagement

Definition:

Public engagement is the interaction between the research team and the community from which the participants are drawn.

Introduction:

Public engagement is a two-way process of dialogue (public – researcher). It improves the community's understanding of the topic, addresses apprehensions and misconceptions and acknowledges the community's input on various aspects, including the social value of the study, research design, participant selection, design of consent processes, information needs, communication processes, compensation and acceptable risks.

Purpose:

To alleviate fears among the public and media, discuss issues such as risk and burdens for participants, emphasize benefits of CHIS, ensure participant safety and correct any erroneous understanding of the research method.

Aims:

- To discuss the scientific and public health value
- To conduct CHIS with public acceptance
- To identify key challenges and concerns of the general public
- To develop strategies to address the challenges

Types of Engagement:

- Public engagement with the larger/ wider group from where volunteers will be sought
- Engagement with specific communities (researchers, regulators, community members, EC members)

Types of stakeholders involved:

Persons from the media (print, electronic and social), professionals, various stakeholders (potential study participants, researchers, EC members etc.), leaders, NGO representatives, government officials, Legal experts, community representatives from the general public.

Methodology:

- Forming Advisory Boards to oversee screening, enrolment and consenting processes.
- Engaging with local representatives for the development of the clinical trial protocols and other preparatory work involved.
- Rigorous screening of participants to ensure compliance with inclusion and exclusion criteria, where a possible large group of volunteers is narrowed down to a smaller number.
- Inviting members of the general public (local media, elders, professionals, government officials, lawyers, teachers, health workers, NGOs, and ECs) to visit the site/ facility.
- Public/ town hall meetings to receive suggestions while discussing protocols, ethical processes, participant selection criteria, consent processes, terms of withdrawal, composition of Advisory
- Boards, payment for participation, compensation and health insurance, long term follow-ups.
- Conducting Open interviews with scientists and the principal investigator, discussion panels, exit interviews with volunteers, online fora and so on.
- Audio-visual/ media aids for improving the understanding of the public about the study and inviting comments from public both in person and through mail/ messages/ electronic/ social media.

Outcome of the engagement activities:

- Enhanced public trust and transparency for the study
- Acceptance of the current and future CHIS, completion of study and avoidance of dropouts
- More altruistic participants to the study
- Development of local facilities

ABBREVIATIONS

BA/BE	Bioavailability/ Bioequivalence
BioRRAP	Biological Research Regulatory Approval Portal
CAB	Community Advisory Board
CDSCO	Central Drugs Standard Control Organization
CHIM	Controlled Human Infection Model
CHIS	Controlled Human Infection Studies
COI	Conflict of Interest
c-GMP	current - Good Manufacturing Practices
CTRI	Clinical Trials Registry of India
DHR	Department of Health Research
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
GEAC	Genetic Engineering Appraisal Committee
GLP	Good Lab Practices
GMP	Good Manufacturing Practice
HMSC	Health Ministry's Screening Committee
IBSC	Institutional Biosafety Committee
ICD	Informed Consent Document
ICF	Informed Consent Form
MoU	Memorandum of Understanding
MTA	Material Transfer Agreement
NABL	National Accreditation Board for Testing and Calibration Laboratories
OECD	Organization for Economic Cooperation and Development
PIS	Participant Information Sheet
QA	Quality Assurance
RCGM	Review Committee on Genetic Manipulation
RCTs	Randomized Controlled Trials
SAE	Serious Adverse Events
SMP	Standard Microbiological Practices
SOP	Standard Operating Procedure

GLOSSARY

Autonomy
The ability and capacity of a rational individual to make an independently informed decision to volunteer as a research participant.

Biomedical and health research
Research including studies on basic, applied and operational research designed primarily to increase the scientific knowledge about diseases and conditions (physical or socio-behavioral), their detection, cause and evolving strategies for health promotion, prevention, or amelioration of disease and rehabilitation (including clinical research).

Clinician
A person with recognized medical qualifications and expertise/ training.

Coercion
An overt or implicit threat of harm to a participant that is intentional to force compliance.

Compensation
Provision of financial payment to the research participants or their legal heirs when temporary or permanent injury or death occurs due to participation in biomedical and health research.

Confidentiality
Keeping information that an individual has disclosed in a relationship of trust and with the expectation that it shall not be divulged to others without permission – confidential.

Deliberate Infection
Deliberate infection involves intentionally introducing a microorganism into an individual's body to study its effects and pathogenesis. This research is conducted under controlled conditions aiming to test treatments and vaccines while adhering to ethical protocols.

Ethics dumping
Ethics dumping refers to the unethical practice of conducting research or experiments, often in a low- or middle-income country, which would not be permissible or would face stricter ethical oversight in a high-income or more developed country. This concept involves the intentional exploitation of research participants and takes advantage of the lack of ethics awareness among researchers or the lower ethical and regulatory standards in the host nation.

Inducement
A motive or consideration that leads one to action or to additional or more effective actions without considering the harm that may occur.

Informed consent document
Written, signed and dated paper confirming a participant's willingness to voluntarily participate in particular research, after having been informed of all aspects of the research that are relevant to the participant's decision to participate.

Legal expert

A person with a basic degree in law from a recognized university and with experience.

Research-related injury

Harm or loss that occurs to an individual as a result of participation research, irrespective of the manner in which it has occurred, and includes both expected and unexpected adverse events and serious adverse events related to the intervention, whenever they occur, as well as any medical injury caused due to procedures.

Risk

Probability of harm or discomfort to research participants. Acceptable risk differs depending on the conditions inherent in the conduct of research.

Sponsor

An individual, institution, private company, government or nongovernmental organization from within or outside the country which initiates theresearch and is responsible for its management and funding.

Stigmatization

Negative perceptions about an individual because of perceived differences from the population at large. It may occur on the basis of physical appearance, race or sex.

Test of understanding

A simple oral or written test designed to identify if the participant has understood the details related to her/his voluntary participation in research before signing the ICD form. (Questions such as “If you decide not to take part in this research study, do you know what your options are?”, “Do you know that you do not have to take part in this research study, if you do not wish to?”, “Do you have any questions?”, etc. will clarify the understanding of the participant.)

Undue Inducement

Offer of disproportionate benefit in cash or kind that compromises judgment which may lead to acceptance of serious risks that threaten fundamental interests.

Vulnerability

Vulnerability in research pertains to individuals who are relatively or absolutely incapable of protecting their own interests because of personal disability, environmental burdens or social injustice, lack of power, understanding or ability to communicate or are in a situation that prevents them from doing so.

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E. Consultations

Insights received during the Indo-US Research Ethics Workshop, Challenging Newer Areas, *ICMR Bioethics Unit, Bengaluru, August 7-9, 2023 wherein around 40 participants participated and deliberated on the various ethical aspects of CHIS.*
Feedback was received from Indo-US Workshop in THSTI, Faridabad *on August 3, 2023, where around 60 participants discussed the ethical conduct of CHIS in India.*
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This policy document attempts to identify the ethical considerations related to the conduct of Controlled Human Infectious Studies (CHIS) in India.

In view of the country's distinctive socio-economic and cultural dimensions with the risk of exploitation of rights, safety and well-being of human participants, it is imperative to put in place measures to safeguard them.

This policy document provides a structure for conducting thorough ethics reviews and identifying ways to navigate through the maze of ethical complexities for quality research outcomes.

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