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

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

Introduction

Controlled Human Infection studies (CHIS) refers to the research methodology that involves intentionally exposing healthy human volunteers to a specific pathogen or infectious agent under controlled conditions. These studies aim to understand disease pathophysiology & immune responses, develop vaccines, test treatment modalities and evaluate the safety and efficiency of potential New Chemical Entities (NCE). In contrast to natural infection studies, which can take longer to observe, researchers obtain data more quickly and efficiently from controlled studies as they involve infecting selected healthy participants under stringent standard protocols. Furthermore, CHIS offers the advantages of accurate observations, comparison and generalization of data as various variables (dose, timing of pathogen exposure etc.) can be modulated. Common types of CHIS include challenge studies, vaccine development trials and treatment studies. Challenge studies involve intentionally infecting healthy volunteers with a controlled strain and a controlled dose to study its host-pathogen interaction, transmission dynamics and potential alternatives to existing interventions. Human challenge studies can accelerate vaccine development by aiding in vaccine selection, by understanding cross-protective immunity, immune correlates & protective mechanisms and by evaluating biologics/ vaccines, while exposing only a small group of volunteers. In comparison to conventional drug trials, CHIS model of assessing the efficacy of drugs may pose a lower risk as these studies use attenuated pathogens to test therapeutic drugs in a controlled environment.

Regardless of the potential scientific benefits, these studies are ethically sensitive and raise concerns about contentious research ethics – such as issues like deliberate harm, possible disproportionate payment and hence inducements, third-party risk, withdrawal from the study and research with vulnerable participants. Hence these studies need a streamlined ethics review process with additional ethical oversight and safeguards to protect the study participants.

This guidance is thus intended to address a variety of ethical issues so that research can be conducted in India without compromising on ethical principles while ensuring the protection of human participants. This guidance in conjunction with the ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017 applies to Institutions, ECs, Investigators, Sponsors and other stakeholders involved in CHIS.
Need for CHIS in India

India carries a high burden of morbidity and mortality from infectious diseases. Infectious disease contributes about 30% of the disease burden in the country. Finding novel, efficient, and cost-effective alternatives to existing methods of research in these diseases and their prevention is imperative to reduce this burden. CHIS is a relatively a new research model that helps provide unique insights into disease pathogenesis and can accelerate the development of novel medical interventions. Though many countries have conducted CHIS research on various infectious diseases such as malaria, influenza, dengue fever, typhoid and cholera, India is yet to conduct CHIS. The deterrents include technical, clinical, ethical and legal contentions, amid unique socio-cultural context. Some potential benefits to conducting CHIS research in India include:

a. Conducting these studies in endemic settings can lead to outcomes relevant to the local population as the participants from endemic areas share similar immunity patterns, associated co-infections, existing pharmacogenomic data, environmental factors, nutrition etc.

b. Vaccine Research uses data related to immune responses in early vaccine development. In CHIS this is achieved by exposing pathogens to only a limited number of participants. Researchers can also assess vaccine efficacy and determine the minimum required dose for protection and immunization in shorter time frames.

c. Researchers can closely monitor the development and progression of an infectious disease from its earliest stages - including symptoms, incubation periods and immune responses -which improves their understanding of the disease. These insights can lead to improved diagnostic methods, treatments and drug development.

d. CHIS can improve understanding of specific aspects of the transmission patterns and/or excretion and/or secretion patterns and dynamics that contribute to the development of effective public health strategies and policies.

e. Conducting CHIS can contribute towards building local research capacities, clinical facilities, laboratory diagnostics, experimental medicine and clinical governance on par with global initiatives on this subject.

Objectives

1.1. To identify the ethical considerations related to CHIS that would guide the protection of safety, rights and the well-being of research participants.

1.2. To provide an ethical framework and a systematic approach for conducting ethics committee review of CHIS-related proposals.
General Considerations

CHIS offers accelerated, cost-effective, and efficient outcomes using smaller sample sizes in comparison to large clinical trials. Its social value includes potential contributions to public health response to diseases of concern, healthcare decision-making, policies & economic benefits—improved pandemic preparedness, and community empowerment.

2.1. Challenge strain

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

2.1.1. Use of well-characterized strains that have been previously used in similar studies is encouraged since such use will provide consistency and allow reliable comparisons to be made. The sequence of the strain should be known so that it is possible to monitor mutations in the future. This can be done in a central lab.

2.1.2. The development of challenge strain requires safe and reliable microbiology and should be in compliance with current Good Manufacturing Practices (GMP) and other regulations as applicable. For these earlier reports of CHIS studies will be useful where characterization of the model strain is mentioned or a reference is given. But broadly, the source of the strain, clade/subtype etc. specifications, full sequence of the strain used, if it is a modified strain such as with a specific gene deletion then the process/method used for deletion and how the deletion was validated needs to be identified. When the same organism is isolated during the course of infection it should be sequenced as far as possible.

2.1.3. Non-clinical lab testing of strains should be conducted in certified labs as applicable. These labs should have safety provisions to avoid contamination to personnel and/ or the community at large. At least Biosafety lab-2 (BSL-2 or higher), standard protocols used for CHIS, specifically trained personnel and Quality Assurance (QA) certificates as applicable are recommended for such studies.6,7

2.1.4. The challenge strain may be genetically attenuated from its wild type (as available in its natural state) to mimic a response similar to natural infection with acceptable risks. Results of preclinical or non-clinical studies of the attenuated organism should be provided with the proposal.

2.1.5. Specific strains may require statutory approvals from various agencies which may include Review Committee on Genetic Manipulation (RCGM) and the Genetic Engineering Appraisal Committee (GEAC) for genetically engineered strains to the extent they are applicable.

2.2. Study design and methodology:

The study protocol should have a scientifically sound research design, methodology, adequate sample size, intervention and control groups, rescue therapy and statistical analysis capable of generating outcomes that will outweigh the potential risks to human participants.
2.2.1. As scientific requirements are unique to each disease, the study design should be specific to the disease. There should be clarity on the potential scientific benefits such as disease understanding, diagnostics or vaccine development, improved treatment and preventive strategies.

2.2.2. Randomized controlled trials (RCTs)/ double-blind procedures are commonly used in CHIS, but with a smaller sample size in comparison to conventional clinical trials, to detect meaningful differences between intervention and control groups. The justification and supporting peer-reviewed literature should be considered when determining the sample size.

2.2.3. As CHIS recruits healthy participants, the study protocol should clearly define the selection and screening criteria for assigning them to intervention and control groups.

2.2.4. Though CHIS has a high component of uncertain outcomes, the study should include anticipated endpoints based on natural infection studies, preclinical studies and/or animal studies. These endpoints include clinical symptoms, parameters for prediction of autoimmunity in pre-clinical and clinical developments, or other measurable outcomes related to the specific pathogen or disease.

2.2.5. The methodology should outline the steps on procedures for inoculating the pathogen, dosing (spike dosing), laboratory investigations, immunological assays, assessment of clinical outcomes, monitoring and any follow-up procedures as they will differ from pathogen to pathogen.

2.2.6. A rescue therapy plan should be in place to address any complications that may arise or adverse events during the study. This includes predefined criteria for initiating appropriate medical interventions and providing necessary medical management to ensure the safety and well-being of the participants.

2.2.7. The interpretation of the results should take into account the unique methodology, potential confounding factors and limitations of the study.

**Responsible conduct of Research**

CHIS must be conducted with the highest level of ethical standards with careful planning, coordination, monitoring and collaboration between various stakeholders. Potential challenges and risks that may arise during the research process should be identified to outline appropriate risk mitigation strategies.

3.1. **Institutional requirements:**

CHIS should only be carried out by institutions that possess the necessary infrastructure, resources, facilities and skilled personnel.
3.1.1. CHIS should only be conducted in centers with extensive experience in conducting clinical trials. These institutions should possess a proven record of academic and research excellence and tertiary-level clinical facilities. The site for the study should be duly equipped with the required budget, space, and infrastructure required for CHIS.

3.1.2. CHIS will be conducted in a closed setting i.e., within a lab/hospital/ research facility where they can be monitored closely.

3.1.3. Institutions must comply with the regulations and guidelines set forth by the appropriate regulatory bodies in India, such as the Central Drugs Standard Control Organization (CDSCO), bio-safety monitoring committee, (including Infrastructure/ environment surveillance), and other relevant authorities.

3.1.4. Clinical facilities and laboratories within the selected institutions should be accredited and enrolled in robust quality assurance programs.

3.1.5. Regular internal audits should be conducted to maintain the highest standards of quality and patient safety.

3.2. Responsibility of Researcher:

Researchers and their team should be adequately qualified, trained, and skilled with prior experience in conducting clinical trials. They must be trained in accordance with Good Clinical Practice (GCP) and ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants.

3.2.1. The researchers are primarily responsible to ensure that the study adheres to the approved protocol, all relevant laws, regulations and guidelines and that all aspects of the research are properly documented and reported.

3.2.2. The researchers must have adequate resources and budgets for conduct of CHIS in order to meet any untoward or unexpected adverse events. Budgetary plans for due ancillary care, medical management, reimbursement of expenses, payment of compensation related to injury, insurance etc. must be in place before any CHIS is undertaken.

3.2.3. Administration of challenge strain should be carried out by skilled and trained personnel to avoid any associated challenges.

3.2.4. CHIS requires both monitoring as well as long-term follow-up of participants therefore, adequate resources should be planned for the same.

3.2.5. Researchers should report any adverse events that occur during the study promptly, maintaining accurate records and data that would be subject to audits by regulatory authorities as per existing guidelines.
3.3. **Collaboration and data sharing**

CHIS is a highly complex area and may require collaborations at different levels between researchers, institutions, organizations and/or between different countries. Collaborations should be encouraged to get the right expertise which may not be available with one center/research team.

3.3.1. Researchers who are new to conducting CHIS may also benefit from participating in collaborative studies with other research institutions. This can be done virtually or physically, depending on the availability of resources and the nature of the collaboration.

3.3.2. It is desirable that the researchers, funders, policymakers and regulators work closely right from the planning process and continue this collaboration throughout the study.

3.3.3. The research team should be aware of all the necessary approvals required for collaborative partnership, which includes memorandums of understanding (MoUs), material transfer agreements (MTA) and EC approval of collaborating institutes.

3.3.4. CHIS may involve the collection of sensitive personal data. This information may be used to create harmful biological agents or to conduct experiments that could be harmful, or could endanger human lives. Hence, access to this data should be limited to relevant personnel from the research team and authorities for the purposes of research alone.

3.3.5. The identified information should be coded or anonymized to protect identity in case data is to be shared. There should be clarity regarding data sharing and preferably a data-sharing policy in line with the applicable regulations and ethical guidelines should be planned. Data should preferably be shared or placed in the public domain in an anonymized form unless required otherwise.

3.3.6. Researchers should strive to publish the results of the study, which may include the characterization of disease outcomes, long-term safety profiles, and insights into the efficacy of interventions. The contribution of all stakeholders involved in CHIS must be acknowledged and respected.

3.4. **Scientific Approval**

3.4.1. Being a new area of research with limited knowledge and experience, it is desirable that a robust scientific review is conducted prior to ethics review.

3.4.2. The proposal must be reviewed through peer review process or undergo a scientific review and approval by an appropriate body/committee which acts independently of the researchers/sponsors supporting this research.

3.4.3. This body could be appointed specifically for the purpose by the academic institutions planning to engage in CHIS and may include subject experts such as immunologists, infectious disease experts, microbiologists, epidemiologists, or others who have the expertise to review and guide the scientific aspects of the studies etc.
3.4.4. The potential conflict of interest in relation to the study, or members of the scientific committee should be appropriately declared and managed.

3.4.5. The comments and suggestions of the scientific committee should be duly incorporated and the revised updated protocol with version number and date as approved by the scientific committee should be submitted to the ethics committee for consideration.

3.4.6. There may be disease specific considerations which must be duly considered and the implications be understood. Table 1 provides a few examples of the type of considerations required as per the subject of research.

**Table 1: Examples of Disease-specific considerations**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Specific Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>• Clinical endpoint, fever or protozoan blood, MP positive, etc.</td>
</tr>
<tr>
<td>Dengue</td>
<td>• No known antiviral, possibility of severe disease</td>
</tr>
<tr>
<td></td>
<td>• Infection of mosquitoes in the community</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>• Transmission to community</td>
</tr>
<tr>
<td></td>
<td>• Airborne transmission, environmental contamination</td>
</tr>
<tr>
<td>Shigella</td>
<td>• Effluent treatment</td>
</tr>
<tr>
<td>Cholera</td>
<td>• Disease Transmission</td>
</tr>
<tr>
<td>Typhoid</td>
<td></td>
</tr>
</tbody>
</table>

5. **Ethical Considerations Specific to CHIS**

CHIS is a relatively new area of research in many countries, including India. The intentional exposure of volunteers to pathogens in order to create a "Human Model" raises unique ethical concerns. Therefore, additional safeguards and oversight to protect participants may be needed. The following points highlight some of the unique ethical concerns:

5.1. **Deliberate Infection**

While such studies may yield valuable insights into the disease pathophysiology and potential treatments, the intentional exposure to pathogens in developing a human infection model for a disease, is considered a contravention of the Hippocratic Oath and violates the “do no harm” ethical code for medical practitioners. The inherent harm owing to methodology includes not only the immediate effects of the pathogen itself but also potential long-term health consequences. Hence the following must be included:

5.1.1. Participants should be provided with detailed information about the rationale and nature of the study, the potential risks and benefits, expected endpoints, treatment plan, duration of infection clearance and measures to minimize harm. There may/ may not be unexpected harm, however, the patient should be made aware of the risk mitigation plan in place.
5.1.2. To minimize harm, the study should be conducted for self-limiting infections and/or those which can be resolved with known medications and treatment protocols.

5.2. Selection of Participants

CHIS is a relatively new research methodology, with a high possibility of uncertain outcomes. Therefore, the selection criteria should be in accordance to the requirements and the scientific design of the study. Some additional considerations are as listed below:

5.2.1. Participants should be in a healthy state and the study should be planned only on adults (18 – 45 years old) unless otherwise justified. A rigorous screening of health status should be employed.

5.2.2. The reason for participation should be evaluated and should include altruism as a genuine desire to contribute to public health advancement, after a thorough understanding of the scientific and social value of research.

5.2.3. Participants should preferably be graduates so that they have the capacity to comprehend the research purpose, potential benefits, and possible harm, allowing them to make an informed decision regarding their participation.

5.2.4. Vulnerable persons are those individuals who are relatively or absolutely incapable of protecting their own interests because of personal disability; environmental burdens; social injustice; lack of power, understanding or ability to communicate or are in a situation that prevents them from doing so and such persons should not be included in CHIS at present. This may be modified at a later stage once Indian institutions and researchers have developed the capacity and experience to conduct CHIS.

5.2.5. Participants with pre-existing medical conditions that may increase the risk should be excluded from the study.

5.2.6. In the present state of knowledge CHIS is not recommended on children as it might endanger their safety. Studies should not be conducted on children at present. However, the document is dynamic and may be reviewed from time to time to include children when deemed appropriate.

5.2.7. 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 foetus. If a female participant becomes pregnant during the study, adequate protection for pregnancy must be taken.

5.2.8. The selection process should be unbiased with regard to gender unless there are specific scientific reasons for gender-based restrictions.

These selection criteria are subject to ethical review and should be based on the needs of the study protocol. These are to be supplemented by other applicable legal and regulatory requirements governing CHIS.
5.3. Benefits and risk

While CHIS may be beneficial for science, the risks to participants may or may not be significant. It is therefore important for researchers, institutions and ECs to undertake a robust, benefit-risk assessment and consider the same from the perspective of the participant.

5.3.1. There are usually no direct individual benefits for participants in these studies, except for the opportunity to altruistically contribute to science.

5.3.2. In some studies, there may be some indirect advantages such as immune protection from exposure to controlled doses of pathogens, since the CHIS agent may stimulate the immune system to protect against future infections. Participants may also benefit from receiving laboratory investigations, ancillary care, counselling or other medical care.

5.3.3. The risks of participation in these studies may be high since participants act as human models to understand the disease progression, transmission and immune responses which expose them to additional risks or discomfort.

5.3.4. There are expected symptoms of the vaccine/ intervention such as mild fever, soreness at the injection site, or fatigue. It is important to differentiate between "expected symptoms", risks and adverse events.

5.3.5. Additionally, there may be other unexpected harm that may include physical injury, psychological trauma, stress, stigma, expenses or loss of income etc.

5.3.6. Prolonged social isolation as required for certain studies may lead to psychological distress such as anxiety, loneliness and depression. Reduced social interaction, separation from loved ones and limited access to emotional support systems can have negative effects on participants' mental well-being. There is a need for physiological evaluation during screening and also for any past history of psychiatric illness and/or anti-psychotic medications.

5.3.7. Cross-infections to third parties such as healthcare workers, family members and household contacts, friends and the community at large could be a significant concern.

5.3.8. There are possible harms related to contamination/ spread to the environment and utmost care may be required to protect against the same.

5.4. Additional safeguards

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

5.4.1. Participants should be provided with healthy meals during the course of the study. Basic hygiene such as clean water, sanitation facilities and other necessities should be available.
5.4.2. 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. Virtual meetings, phone calls, or video conferences, recreational and leisure activities, use of multimedia such as television, radio, and music may be used to help them relieve stress and maintain a positive mental state. There should be honest communication and explanation of procedures, expected physical responses and discomforts.

5.4.3. Participants should have access to mental health professionals who can provide support and counseling throughout the study.

5.4.4. Healthcare workers are at high risk of contracting and transmitting infections and therefore must undergo regular health screening.

5.4.5. All involved personnel must be adequately trained in infection control measures and provided with the necessary protective equipment to protect themselves and also to prevent the spread of infections.

5.4.6. Family members and other visitors to the healthcare facility should also be screened to prevent the spread of infections.

5.5. **Informed Consent**

Informed Consent refers to the process of full disclosure of the nature of the research and the participant's involvement that ensures adequate competence, comprehension and voluntariness through which participant provides a free choice or agreement to participate without any coercion or influence. The Informed Consent Document (ICD) should consider local, social and cultural contexts depending on the type of CHIS and the study design so as to ensure that the ICD process is relevant, understandable and respectful towards the individuals and communities involved. The content of the informed consent should be in line with ICMR National Ethical Guidelines 2017, particularly Section 5. In addition, the following points should be considered.

5.5.1. Written informed consent and, when applicable, consent for audiovisual (AV) recording should be obtained. Specific requirements for obtaining informed consent and AV recording consent can vary depending on local regulations, institutional policies, and the nature of the study or procedure.

5.5.2. Researchers need to dedicate time and effort to explain and ensure understanding as participants may not fully understand the nature of research, the potential risks and requirements of participation due to the complicated nature of study design. Thus, there should be a focus on comprehension and capacity of an individual, and assessing the voluntariness for obtaining valid informed consent from CHIS participants.

5.5.3. The form should have a clear statement that the CHIS is a research study that involves deliberate exposure to an infectious agent in order to have a human disease model.
5.5.4. As the study involves deliberate harm and higher risk, it is an ethical requirement that these aspects should be clearly explained to the participant in a simple form and manner, and in a language in which the participant has a full understanding about the research.

5.5.5. Participants must have a clear understanding of the purpose and procedures of the study, along with anticipated risks and benefits as well as available rescue treatment and procedures. The alternative to participation is not to participate and if they participate, they will receive a standard of care as appropriate for the disease under study. Participants must have the opportunity to ask any questions, as well as discuss with their family and friends which can be documented. The process may include detailed one-to-one interactions and small group discussions with the volunteers and if the participant wants, may also involve others from their immediate families to understand all aspects of the study. Adequate time for comprehension of information needs to be provided to the participants before their consent is taken.

5.5.6. The researcher must evaluate the true nature of altruistic motives to participate and select only altruistic participants that meet the selection criteria of the study.

5.5.7. Researchers must ensure there is no undue inducement or coercion that would have influenced the volunteers’ decision. If these are detected, the participant need not be included.

5.5.8. A test of understanding (open ended set of questions) could be framed in order to make sure the comprehension of the study is adequate [See Annexure 3]. To clear this test a minimal level/score has to be predetermined by the researchers (and approved by the EC). Only those who are able to prove their adequate understanding may be recruited.

5.5.9. The information on payment for participation, reimbursement of the expenses borne, compensation and medical management for research-related injuries, as well as the need for long-term follow-up should be mentioned in the consent form. The exact amount of payment for participation must be revealed only after the volunteer has consented to participate. Investigator should strive to reveal the payment only after the participant consents.

5.5.10. The researchers must explain and discuss all components of the Participant information Sheet and Informed Consent Form to the participants and make efforts to build trust and better understanding - which would in turn help to improve compliance leading to better cooperation and improved research outcomes.

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

5.5.12. Consent form elements and additional considerations are given in the table below.

Table 2: Elements of Informed Consent Form
<table>
<thead>
<tr>
<th>Basic elements</th>
<th>Additional considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statement about the research study and need for altruistic participation</td>
<td>Motivation to participate / Participant selection criteria</td>
</tr>
<tr>
<td>Purpose, Procedures and Duration of the Study</td>
<td>Potential risks and burden to individual and community</td>
</tr>
<tr>
<td>Duration of participation and type of data collection/ procedures</td>
<td>Withdrawal and third-party transmission/ Alternate treatment approaches</td>
</tr>
<tr>
<td>Benefits and Possible outcomes for individual/ family/ science</td>
<td>Psycho-social support/ management/Counselling if any</td>
</tr>
<tr>
<td>Foreseeable risks/ harms/ inconveniences/ Mitigation plans</td>
<td>Possibility of stigmatization/ long term effects (for e.g., immune status)</td>
</tr>
<tr>
<td>Privacy and Confidentiality of identified information</td>
<td>Need for AV recording of informed consent process</td>
</tr>
<tr>
<td>Reimbursement of costs &amp; Payment for participation</td>
<td>Declaration of payment amount only after informed consent to participate is obtained</td>
</tr>
<tr>
<td>Medical management/ Compensation for related injuries/ Insurance</td>
<td>Storage and transfer of biological materials/ data</td>
</tr>
<tr>
<td>Freedom to withdraw and the limitations upon participation</td>
<td>Post-study plan/benefit sharing</td>
</tr>
<tr>
<td>Contact Information of study team / ethics committee</td>
<td>Dissemination /Publication of results</td>
</tr>
<tr>
<td>Study Monitoring</td>
<td>Long Term Follow up</td>
</tr>
</tbody>
</table>

5.6. **Privacy & Confidentiality**

CHIS involves sensitive data which may have implications towards participants' health and well-being as there is a risk of social stigmatization. The data that is collected should be limited to the purposes of the study.

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

5.6.2. In the case of CHIS, the data may require long term storage and therefore, confidentiality. Data protection measures must be taken appropriately and informed to participants prior to their recruitment in the study.

5.6.3. If the identified data is to be published or shared with collaborators, appropriate permissions, consent, ethical approval from relevant authorities along with any other requirements to safeguards participants must be in place.

5.7. **Payment for Participation**

Participants may incur costs due to their participation in CHIS and this could include loss of wages (for the time spent in isolation), transportation and/or other incidental expenses. They may therefore receive
an amount of payment as reimbursement in addition to the payments made recognizing the time spent
and efforts made while participating in CHIS. The following needs to be considered:

5.7.1. The inconveniences and discomforts due to participation in CHIS are expected and maybe
significant as it involves isolation, symptoms related to immune responses (nausea, vomiting,
myalgia, fever etc.) and needs to be medically managed. These expected symptoms will not
qualify as adverse events/ severe adverse events. Hence, the payment should commensurate with
the inconvenience and discomfort that are expected.

5.7.2. Provisions for reimbursements of any incurred expenses should be in place and budgets should
be accordingly built into the protocol.

5.7.3. An additional payment may be made for participation, which could be made in cash or kind.

5.7.4. Payments other than reimbursement of costs should preferably not be disclosed prior to
recruitment in order to avoid any possibility of inducement.

5.7.5. All such payments and/or free services provided to the participants should be reviewed by the
ethics committees prior to initiation of research.

5.8. Monitoring and Follow-up of Participants

CHIS may require independent monitoring due to the deliberate exposure of pathogens. Additionally,
monitoring may be done at different levels - self-assessment by researchers, institutional authorities,
ethics committees, sponsors and regulatory bodies. These could be in the form of site visits, follow-up
calls, regular reporting and inspections.

5.8.1. Research participants should undergo periodic health assessments at predetermined intervals
following the initial study. These assessments may include physical examinations, laboratory
tests, imaging studies, and questionnaires.

5.8.2. The length of follow-up varies depending on the pathogen and requires monitoring for 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.

5.8.3. Researchers must take all necessary precautions to prevent the spread of the pathogen beyond the
study population to household contacts, community and similar. However, any symptom
developed by the third party due to the exposure by the participant(post-study) must be reported
immediately and arrangements for medical care must be made.

5.8.4. Participants should be regularly updated on the progress of the study, any new findings which
emerge, and the potential implications towards their health.

5.8.5. Some participants may require long-term psychological support, counselling services, or referrals
related to stigma/ social isolation/ or psychological distress.
5.8.6. In addition to monitoring by the research team, there should be regular monitoring planned by the Sponsors, Data and Safety Monitoring Boards, Ethics committees, regulators (if any) to ensure the robustness of conduct of study and the safety of research participants’ health, safety, wellbeing and rights in research.

5.9. **Compensation for research-related harm**

The unexpected or unknown harms/risks associated with participating in CHIS may be significant and therefore there should be appropriate provisions to cover insurance and provide for medical management and compensation for research related harm and injury. The Drugs and Cosmetics Act, 1940, read with the NDCT Rules, 2019, governs the conduct of clinical trials as well as biomedical and health research. The rules contain detailed provisions regarding regulatory approvals, ethics review, and provisions for the protection and safety of participants. Chapter VI of the NDCT Rules, 2019 contains provisions for medical management and compensation in case of injury or death in clinical trials or bioavailability or bioequivalence studies. This Chapter will apply to CHIS that involves testing new drugs or vaccines. Biomedical and Health Research is subject to Rule 45 of the NDCT Rules, 2019. It states that medical management and compensation for injury or death will be governed by the ICMR National Ethical Guidelines 2017. In addition to this, Rule 16(4) of NDCT Rules, 2019 specifies that all research must be conducted in accordance with the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017. Consequently, researchers have a legal obligation to ensure that their work adheres to these guidelines, as well as to the appropriate provisions of the NDCT Rules.

5.9.1. The research study should provide health insurance cover for all participants during the study as well as for the follow-up period. Insurance could also be planned for the third parties (family/ lab personnel), depending on the nature of infective organism or where the risk is higher. The provisions for insurance should be made through companies with offices based in India.

5.9.2. Study expenditure, costs related to ancillary care, medical management and compensation should be built into research grants, insurance or corpus funds established by the sponsor/institution/researcher.

5.9.3. The local ethics committee is responsible for reviewing the relatedness of the SAE to the research and determining the quantum and type of assistance to be provided to the participants as per the NDCT Rules, 2019. As per SOPs, the ethics committee may plan to set up a SAE subcommittee for causality assessment to carefully review the adverse events that are reported.

5.10. **Post study access/benefit sharing- opening statement**

There may or may not be clear and direct benefits of participation available immediately, however in case there are, the following may be considered -
5.10.1. Participants who have undergone experimental interventions or treatments should have access to any direct or indirect benefits of the study.

5.10.2. There should be information regarding how participants will receive any benefits from royalties, patents or commercialization of the drug/treatment/vaccine involved in the intervention, if any.

6. Ethics Committee Considerations

6.1. Roles and Responsibilities

The EC reviewing CHIS should follow the roles and responsibilities of ECs outlined in the ICMR National Ethical Guidelines 2017 with the following additional considerations:

6.1.1. EC may have limited scientific understanding to review studies involving creation of a human model and may consider co-opting one or two subject experts who can help to improve the ethics review process. Independent consultants with relevant expertise may be identified and invited by the EC secretariat in consultation with the chairperson.

6.1.2. Since there is a possibility of harm related to deliberate infection, scientific review is of great importance. The comments and suggestions received from the scientific committee must be closely reviewed by scientific members (clinicians and/or basic scientists) to see if the protocol has incorporated all suggestions and is well designed with an appropriate methodology, sample size and selection of sites and investigators. Further, the committee should do benefit-risk analysis, review the study plan, plan for isolation, reporting of AEs or SAEs, provisions for medical management, compensation in case of injury, payments for participation involved and the possible long-term implications along with any other considerations.

6.1.3. Non-medical members such as social scientists/ethicists and others should thoroughly review the proposal, taking into consideration both the participant's and the public's perspectives. In addition to this comprehensive ethics review, the socio-cultural context and the potential long-term implications of CHIS, which includes social isolation and psychological distress would need due consideration.

6.1.4. The legal expert/s should assess the study's compliance with existing laws, rules, regulations and guidelines. They may also look into the prospect of deliberate infection and its implications, availability of insurance schemes, agreements, other regulatory approvals or permissions, collaborative arrangements, data sharing and transfer to biological material or data.

6.1.5. The lay persons would have an important reviewer bringing out the community and social perspective from the participants’ point of view, built-in provisions for public engagement or plans towards building trust.
6.1.6. All members should have an adequate understanding of the ethical and legal implications of the study. The EC members must be specifically trained to improve understanding and updated on a timely basis regarding rules/ regulations/ guidelines related to CHIS.

6.2. Ethics Review

CHIS should undergo an initial, full committee review as per the ICMR National Ethical guidelines by the ethics committees at the participating study sites.

6.2.1. The EC should determine the completeness of submission including statutory approvals required for conducting the study, Scientific Committee approval, protocol updation based on the recommendations of scientific committee and the fulfilment of other requirements as per the ICMR common forms.12

6.2.2. The ethics committee must undertake the review in a full committee meeting deliberating upon the ethical issues as discussed in Table 3 below.

Table 3: Framework to guide the ethics review

| Social Value | • Adds value to public health/ existing policies  
| • Aids in reducing the burden of existing endemic disease (improved knowledge/new therapeutics/vaccine).  
| • Reduces economic burden of the disease |
| Scientific review | • Prior scientific review done  
| • Approval/ minutes of scientific review is enclosed |
| Researcher Competence and Experience | • Ethics and GCP training  
| • Relevant experience in clinical trials  
| • Specific training/experience to conduct CHIS |
| Institution | • Adequate logistics and infrastructure for CHIS  
| • Trained manpower to conduct CHIS  
| • Isolation facilities and recreational provisions  
| • Budgets to handle any adverse events |
| Participants | • Only healthy adult, preferably graduate volunteers  
| • Altruistic  
| • Age between 18-45 years, unless justified  
| • Exclusion of vulnerable population (children/pregnant and lactating women/marginalized communities, others) |
| Benefit and Risk assessment | • Individual benefit/ benefit to science / society/ creation of new knowledge  
  • Risk of developing unexpected symptoms due to exposure of challenge strain.  
  • Procedural risks  
  • Risks associated with treatment of challenge infection (such as the use of antibiotics) or treatment failure.  
  • Risks of psychological harm (such as adverse effects of isolation on mental health)  
  • Risks of social harm (such as stigmatization)  
  • Risk of third-party infection (research staff/ family/neighbors/ community).  
  • Environmental risks (such as contamination of effluent water). |
|---|---|
| Consent Process | • Basic elements of consent are present (Table 2)  
  • Consent form in simple language/ understanding  
  • Time/ space/ counselling/ adequate time for discussion/ who conducts consent process  
  • Test of understanding  
  • Payment for participation to be revealed after consenting  
  • Requirement of isolation and possible quarantine and withdrawal restrictions  
  • Long term follow-up, if necessary  
  • Need for Audio Visual recording of Consenting |
| Protection of privacy and confidentiality | • Access of data to restricted personnel  
  • Highest confidentiality measure (to avoid stigmatization)  
  • Only necessary and proportionate collection and disclosure of data  
  • Data Sharing plan/ policy |
| Payments for participation and Reimbursement | • No undue inducement  
  • Reimbursements proportionate to the loss of time/ wages/ incidental expenses only  
  • Payment amounts to be reviewed |
| Compensation for research-related injuries | • Provisions made to address research-related harm (injury related to CHIS)  
  • Insurance/ grants/ medical management  
  • Extended coverage to third parties |
| Fair collaborative arrangements | • No additional risk in conducting it in India or anywhere else in the world.  
  • Agreements/ Plan for return of research results/ data sharing/ publications |

6.2.3. The Chairperson must seek a conflict-of-interest declaration from all members before the start of the review process since there may be financial or non-financial conflicts of interest.
6.2.4. In order to address the potential involvement of multiple stakeholders with commercial interests at various levels, EC should review the study and propose methods to mitigate the same at the level of researchers/ institutions.

6.2.5. The ethics committee may suggest the need for public engagement, community sensitization, and review the plan for community engagement and advocacy, social media or other approaches to order to build public trust. If required, it may recommend the need to establish a community advisory board for the study.

6.2.6. EC is also responsible for ensuring that the participants are not exposed to unnecessary risks and that the study is conducted in a manner that minimizes potential harm. Regular reporting of adverse events and serious adverse events in a manner as provided under the New Drugs and Clinical Trials Rules, 2019 and 2023.

6.2.7. EC is responsible for monitoring the study's progress, reviewing the data collected and ensuring that the study is conducted according to the approved protocol. EC should therefore have a robust system for continuing review of the implemented studies, including on-site visits and long term follow-up of the study. The EC may plan an oversight committee which includes external members/international experts.

6.2.8. Researchers and institutions may be liable for any harm caused to participants/third parties as a result of the research. Therefore, it is essential that appropriate measures are in place to minimize the risk of harm and those participants are provided with adequate medical care and compensation if needed.

6.2.9. In light of the potential risks associated with exposure to infectious agents, these studies have an elevated probability of harm. Establishment of a subcommittee is recommended to closely monitor and review any SAEs that may arise. This committee should consist of two or more members who possess the necessary knowledge and expertise to review SAEs in the context of CHIS.

6.2.10. EC should review the necessity of maintaining a distinct Data and Safety Monitoring Board (DSMB) for close monitoring and evaluating the progress of the study, conducting interim data analysis, and disseminating the finding. The DSMB is responsible for monitoring the safety and efficacy of a clinical trial and must ensure the safety of research participants by reviewing the data collected during the trial and for making 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. Furthermore, the EC may also seek reports on monitoring activities conducted by both the sponsor and the DSMB.
6.2.11. In case of use of organism/ recombinant/ bioengineered CHIS agent, an Institutional Biosafety Committee must review in compliance with the Guidelines and Handbook for Institutional Biosafety Committee, as issued by the Department of Biotechnology, and as required under the Rules for the Manufacture, Use, Import, Export and Storage of Hazardous Microorganisms/Genetically Engineering Organisms or Cells, 1989.

6.2.12. In case a common review is planned for multicentric CHIS study, a comprehensive common review may be conducted. However, it needs to be ensured that the local ECs at the participating sites have thoroughly reviewed the research proposal in light of the site-specific requirements and institutional preparedness to conduct the research and monitor the same. Participating site ethics committees can establish a robust communication system to facilitate efficient coordination and enhance the overall quality of ethics review process and to conduct the same in a timely manner.

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

7. Advocacy, Public Engagement and Public Trust:

As CHIS involves the deliberate infection of healthy volunteers with a pathogen, advocacy is important in building public trust and gaining confidence in research. It entails research group education as well as listening and clarifying the public’s understanding of the research, addressing misconceptions and acknowledging the public’s input on the social value of the study.

7.1. Researchers must conduct public engagement to alleviate the fear among public and media and to correct erroneous understanding of method of research through discussing scientific rationale, selection process, procedures of the study, anticipated risks involved, benefits, participant safety, alternative treatments, design of consent processes, protective measures, compensation for research-related risk, terms of withdrawal, long term follow-ups etc.

7.2. Persons from the media (print, electronic and social), various public / stakeholders (potential study participants, researchers, ethics committee members and so on), professionals, leaders, NGO representatives, government officials, legal community, should be invited for public engagement.

7.3. Researchers should promote public understanding and acceptance of CHIS through educating and engaging with representatives. Research team need to make efforts to build dialogues/interaction with the public from which the participants are drawn and attempts should be made to resolve differences of opinion with representatives/stakeholders through respectful approaches. The engagement process involves:
7.3.1. Advisory Boards consisting of representatives from both the research team and the public to oversee the following screening and enrolment and consenting processes.

7.3.2. Engaging with local representatives to invite volunteers to discuss on the preparatory work involved as well as development of the protocols and participant safety measures. Public / town hall meetings involving local media may be arranged to receive suggestions.

7.3.3. Communicating information such as investigator competencies, funding, insurance, conflicts of interest, collaborating countries and institutions by researchers.

7.3.4. Obtaining feedback on research proposals from representatives to identify potential ethical concerns.

7.3.5. Delivering information through media about the intention to conduct study and inviting comments from public both in person and through mail/ messages/ electronic/ social media.

7.3.6. Improving public understanding of the study through audio-visual aids.

7.3.7. Conducting open interviews to capture participants 'experiences to ensure trust and transparency in a respectful and informative manner. This may be shared on public platforms. However, anonymity, privacy and confidentiality have to be maintained.

7.3.8. Making arrangements to receive and respond to doubts / queries / complaints/ request for site visits preferably through a website/ webpage/ blog set up for the specific CHIS.

7.3.9. Providing clear and concise information to media and ensuring accurate, responsible and balanced reporting of CHIS enhances public trust.

Table 4 outlines points that may be considered when addressing advocacy and building public trust.

| Indemnification/ Insurance of the facility/study side/researchers/participants |
| Communication systems such as a website, information board outside the facility, leaflets/ brochures, Q&A boxes, Contact detail displays, Site visit days |
| Quality Control Policy / Procedures. |
| Publication and dissemination protocols of the results and lessons learnt including mistakes and negative results. |
| MOUs and service contracts will all collaborators/service providers. |

As CHIS raises potential apprehension among the public, all these efforts help to build public trust and transparency, acceptance of the current and future CHIS, more altruistic participants in the study and development of local facilities.
Research Governance and Other Considerations

There are specific ethical issues related to CHIS which necessitate the requirement of policy statement on the governance aspects of conducting the study, to ensure participant and community safety. For the conduct of all kinds of CHIS, the following conditions must also be met:

8.1. Compliance with current Good Manufacturing Practices (C-GMP) for the use of challenge strain and as required under the New Drugs and Clinical Trials Rules 2019. This includes registration of the study on the Clinical Trials Registry-India.

8.2. Participating labs should have compliance with GLP as prescribed by Organisation for Economic Co-operation and Development (OECD). These laboratories may be accredited by National Accreditation Board for Testing and Calibration Laboratories (NABL).

8.3. Biosafety level certification of the laboratory, as required under the Guidelines for the establishment of Containment Facilities: Biosafety Level 2 (BSL-2) and 3 (BSL-3).

8.4. Compliance with Regulations and Guidelines for Recombinant DNA Research and Biocontainment, 2017, to the extent that they are applicable to the challenge strain.

8.5. Approval of an Ethics Committee registered in accordance with the New Drugs and Clinical Trials Rules, 2019.13,14

8.6. In the case of international collaboration or funding, clearance may be required from the Health Ministry’s Screening Committee (HMSC) or from BioRRAP in case it is applicable.

8.7. All regulatory approvals needed for the conduct of the CHIS in question need to be obtained and copies of such approvals to be forwarded by the investigator to the Central Drugs Standard Control Organisation (CDSCO). These approvals include Rules for the Manufacture, Use, Import, Export and Storage of Hazardous Microorganisms/Genetically Engineering Organisms or Cells, 1989, issued under the Environment (Protection) Act, 1986. Compliance with these Rules will require permission from the Review Committee on Genetic Manipulation (RCGM) and the Genetic Engineering Appraisal Committee (GEAC), as applicable.

9. References:


3. National Ethical Guidelines for Biomedical and Health Research involving Human Participants. New Delhi: Indian Council of Medical Research; 2017. Available from:


13. Naitik Portal for National Ethics Committee Registry for Biomedical and Health Research (NECRBHR) under the Department of Health Research (https://naitik.gov.in/DHR/Homepage ) (accessed 03 Jul 2023)

Annexures
Annexure A – Public Engagement

**Definition:**

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) which improves community’s understanding on the topic, addresses apprehensions and misconceptions, acknowledges the community’s input on social value of the study, aspects of research design, selection of participants, design of consent processes, information needs, communication processes, compensation and acceptable risks.

**Purpose:**

To alleviate the fear among public and media, to discuss issues (risk and burdens for participants), benefits of CHIS and participant safety, and to correct erroneous understanding of method of research.

**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, ethics committee members)

**Types of stakeholders involved:**

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

**Methodology:**

- Forming Advisory Boards to oversee screening and 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.
**Community Consent:**
Community consent may also be considered as there are risks of third-party infection and stigmatisation of participants once they return to the community.

**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

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**Annexure B – Informed Consent**

**Definition:**
The process of full disclosure of the nature of the research and the participant’s involvement that ensure adequate comprehension associated with the particular study/intervention through which participants provide their voluntary choice/agreement to participate.

**Introduction:**
Seeking valid consent from CHIS participants through contextualised consent procedures is an ethical requirement because participants may not fully understand the potential risks and obligations of the participant or may be vulnerable to undue inducements or coercion.

**Purpose:**
To ensure that participants are fully informed and have a clear understanding of the purpose and procedures of the study, anticipated risks and benefits and available alternative procedures and/or 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**
- Ensuring the participant’s comprehension and understanding.
- Allow for them to ask questions. Allow for them to consult with family doctor, relatives and community members.
- Sufficient information provided to the participant in a language that they can understand.
- Ensuring altruistic and voluntary participation.

**Additional considerations for CHIS**
- Participant selection criteria
- Withdrawal and third-party transmission
- Possibilities of isolation and quarantine
- Alternate treatment approaches
- AV recording of the consent
- Declaration of payment amount once consented
- Storage and sharing of data and biological materials
- Extent of maintaining privacy and confidentiality
- Post-study plan/benefit sharing and participant follow up post the completion of the study.
- Dissemination/Publication of results.

**Informed Consent Process:**

- Selection of the right individuals to participate in CHIS - choosing altruistic and literate participants from middle and upper socio-economic strata of the society.
- Detailed one-to-one interaction with the volunteers and their immediate families (where relevant) and disclosing all information about a study.
- Detailing the need for long-term follow-up if required.
- Providing information on payment for participation and compensation for research related injuries.
- Payment for participation will be revealed after the study volunteer consents to participate.
- Providing opportunity for the participants to discuss with family and friends before they consent.
- Administering a test of understanding to evaluate whether the participants have fully understood the study. Test of understanding needs to be prepared specific to the type of CHIS.
- Educating the risk of third-party transmission and infection control measures upon withdrawal from the research.
- Audio-visual recording of the informed consenting process.
- 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 who come into close contact with the study volunteer.
- The participant should be fully informed about the consequence of withdrawal from the study, or the extra precautions that may be required if premature withdrawal is unavoidable. The participant should be made aware that in case of withdrawal (either voluntary or at investigator’s discretion), the participant may have to undergo confinement for a quarantine period.
- The consent process should emphasize this difference in withdrawal from CHIS as opposed to other clinical trials in case of withdrawal (either voluntary or at investigator’s discretion)- that the participant may have to undergo confinement for a quarantine period. Also it may be mentioned that if the study has reached a certain stage, withdrawal may not be possible further.

**Outcome:**

- Enrolling fully informed study participants.
- Protection of participant autonomy in enrolling to the study that requires intentional harm.
Annexure C – Test of Understanding

**Definition:**
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.

**Introduction:**
Informed consent is a critical component of biomedical health research, yet participants’ comprehension of the information offered is frequently inadequate. During consenting procedure, it is necessary to test the level of understanding of the prospective study participants to check whether they 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:**
- Extended discussions with the participant and should ask about the study. The participant must be able to describe the study, associated risks and expected requirements for participation.
- Test quizzes can also be used to evaluate the participant's understanding. The questions must be framed in such a way that it will check the participant's understanding about the method of study, intentional harm, expectations from the participants, withdrawal procedures, risk of third-party infection, the possibility of isolation etc.
- The questions/ tests should be open ended to help improve the process by giving an opportunity to the participant to express information as per their understanding.

**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.