16th August 2023

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

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On 17th July 2023 the ICMR released a Consensus Policy Statement for Ethical Conduct of Controlled Human Infection Studies (CHIS) (hereinafter referred to as "the Statement), inviting comments from the public within a month.

The Statement lacks clarity, and proposes low standards for the conduct of CHIS, with potential to exploit vulnerable people and violate human rights. It needs to be redrafted incorporating high scientific and ethical standards and protection for participants and society.

GENERAL CONCERNS

1. The Statement lacks transparency and accountability of the drafters. When a document has been placed for public review, the reviewers ought to know the names of individuals who drafted the document, all those who have been consulted, those who will take the reviewers' comments into consideration, and whether reviewers will be informed of the reasons for accepting or rejecting (partially or fully) their comments.

2. The Statement gives the impression that it is based on the ICMR's recent consultation with a few experts without taking into consideration deliberations of over half a decade on CHIS sponsored by the Translational Health Science and Technology Institute (THSTI) of the Department of Biotechnology (DBT) and the ICMR. It cites only one paper by Vaz et al [1] when there is much more literature on developing scientific and ethical standards for CHIS in India.[1]

3. The Statement contains many vague or general assertions and suggestions, allowing loopholes, and leeway for legal and ethical violations. Expressions such as "as far as possible", "will be useful", "may be", "encouraged" or "recommended" appear all through the document, instead of stringently laid specifications.

4. There are many contradictory points. Definitions of the terms used are not provided. The language is neither gender inclusive nor inclusive of divergence in abilities (eg persons with

[1] For example, THSTI/DBT with the ICMR and the Tata Institute of Social Sciences organized a multi-stakeholder consultation in January 2018, to deliberate on the ethics of CHIS in India. That resulted in the publication of six papers [2-7] in the theme issue of the *Indian Journal of Medical Ethics* titled "Developing the Ethics of Controlled Human Infection Models in LMICs" and an editorial [8], which together clearly outline social value considerations and the gaps in the current ethics and legal framework in India to be addressed if such studies are undertaken. Some more literature was also published in the *IJME* thereafter and the TSHTI also had some more consultations.

disabilities) and various other vulnerabilities.

5. The Statement does not provide any information on the capacity, effectiveness and efficiency of current regulatory mechanisms for clinical trials. The problems of the Central Drugs and Standard Control Organization (CDSCO) in regulating the quality and prices of drugs, as well as clinical trials, and its shortage of staff and funds, are well known. There are also concerns about the quality of inspection of Ethics Committees registered with CDSCO and the Department of Health Research, and the absence of rigorous oversight of their functioning. A guidance for undertaking new high-risk research must include an assessment of the governance capacity and efficiency of the implementors, and a strategy for optimization / augmentation.

6. The Statement does not prescribe any accountability for violations, in processes or in care for participants, by researchers, institutions and sponsors/funders conducting CHIS.

CHIS AS A NEW RESEARCH METHOD: STRENGTHS AND LIMITATIONS

1. The Statement creates an environment of complacency when what is needed is caution, a much higher level of due diligence in decision making regarding the use of CHIS, and **care and protection** of trial participants when conducting CHIS. Procedures for deliberate infection introduce harm in healthy individuals for experiment, which have potential to result in injury or death, solely due to the research.

2. Throughout the Statement CHIS is described as "novel, efficient, and cost-effective alternatives to existing methods of research" that "in comparison to conventional drug trials, CHIS model of assessing the efficacy of drugs may pose a lower risk". **The Statement must clearly explain the limitations of CHIS.**

3. The Statement does not explain that CHIS is carried out in two stages. In the first stage, in controlled conditions, healthy human volunteers are infected with a highly attenuated strain of an infecting pathogen (challenge strain) to cause a relatively mild form of infection or disease. The deliberately produced disease is then studied to understand the process and pathophysiology of the disease caused by this challenge strain. This is called development of the Controlled Human Infection Model (CHIM) for that disease. Once the CHIM for a disease is established, in the second stage healthy participants are used to test a new drug or vaccine candidate. When testing a new therapeutic drug, healthy participants are first infected with a challenge strain and then randomized (with double blinding) to receive either the new drug or the currently available best drug (or, if no treatment is available, a placebo). The two arms are then compared to assess the drug's capacity to treat the challenge strain. In the case of a vaccine study, healthy participants are randomized (with double blinding) and those in the experimental arm are given the vaccine candidate, and those in the control arm are given the currently available vaccine or a placebo; all of them are then infected with the highly attenuated strain of the pathogen. The two arms are then compared to see who develops the disease.

4. From this it will be evident that **participants in a CHIS are exposed to both the risks of deliberate infection and the classical risks of drug trials, doubling their risks.** Unfortunately, the Statement, by not explaining how such studies are carried out, and by calling them easier and "more efficient" than conventional methods, suggests that CHIS studies are lower risk.

5. Conventional clinical trials of drugs go through three phases. In Phase 1, new drugs and vaccines are tested for the first time in humans, on healthy participants. **Phase 1 trials are required even for drugs and vaccines developed using CHIS.** As CHIS tests efficacy in smaller numbers, it can best be used by Phase 2 testing of many candidate drugs/vaccines. But **CHIS does not eliminate the need**

for large Phase 3 trials in natural conditions; as it does not use the naturally occurring pathogen but its highly attenuated variant, there is no guarantee that a drug or vaccine developed in controlled conditions will be as efficacious in natural conditions. The Statement understates and overlooks this significant limitation of CHIS.

6. There is a need to produce data supporting the statement that CHIS is "cost-effective". In fact, there are no Indian data to support such a claim. Such a claim would require estimates of the cost of developing and establishing a sustained production line for high-quality attenuated challenge strains of the pathogens of interest for our country, using international standards of Good Manufacturing Practices (GMP). It should also include the costs of investment and maintenance of sophisticated infrastructure, a controlled environment, and additional trained health personnel. There are cost estimates from high-income countries. However, as these countries do not find such infections in their society, their "cost effectiveness" assessments will be relative to the cost of getting such studies done in the community. For India, such infections are found in the community, so the cost of conventional studies may not be as high in comparison.

Format for General Comments/Suggestions (if any):

Sections	Comments/ Suggestions
Section 1 - Introduction	**<u>Section 1 – Introduction and Need for CHIS in India</u>** *General Comments:* A. The Introduction refers to CHIS as a relatively new research method. However, systematic controlled infection studies are several decades old, and both their scientific and ethical problems are well known. B. The Introduction section does <u>not clearly explain in detail</u> the **two stages of CHIS**. It must also clearly state that CHIS **involves "double risks"** – those arising from deliberate infection, and those of conventional drug/vaccine trials. It does not clearly state the limitations of CHIS, including that it does not necessarily eliminate the need for large Phase 3 trials. C. The Statement **overestimates the benefits** and **underestimates the risks** of CHIS, providing a one-sided picture of benefits and advantages, creating an environment of complacency when what is needed is caution, and much higher level of care and protection in doing CHIS. *Specific Comments:* A. The Statement should explain **what is unique about CHIS that provides better insight** than the normal infection process. B. The statement should explain in **what way CHIS offers advantages** of accurate observation, comparison, and

	generalization of data, as modulations of variables – such as dose and timing – in a way **that is not possible through conventional Phase I to III clinical trials**. C. The statement should explain what **value addition CHIS would provide for infections/ diseases in India**. F. With reference to p.3 (a) that conducting CHIS in endemic settings can lead to outcomes relevant to the local population, the statement should explain **why, if a disease is endemic in India, we should prefer CHIS over conventional methods.** G. The Introduction does not state clearly **which infections/ diseases will be studied using CHIS, and for which it *ought not* to be conducted in India** -- because they are not necessary, or they are dangerous, or not treatable, or any other reason. This is necessary to **ensure that there is no "ethics dumping" with CHIM** being used in India on diseases of concern in high income countries, as happened with conventional clinical trials. H. Lastly, **specific details of the kind of facilities required** for medical facilities for conducting CHIS are required. We have not built adequate institutional capacities for conducting Phase 1 trials, and CHIS will demand facilities of higher physical, medical and healthcare human resources standards than those for Phase 1 trials.
Section 2 - Objectives	**<u>Objectives are Section 1.</u>** The Statement must include **clear Objectives and Rationale** that bring out the intent and purpose of bringing out these guidelines. The Statement's objectives currently are limited to guidance for ethics review by Institutional Ethics Committees (IECs). It **does not provide guidance about the higher standards of review needed for CHIS**. The objectives do not include the essential elements/ standards relating to monitoring of CHIS, mandatory onsite monitoring by the IEC, and mandatory requirement for a Data Safety Monitoring Board (DSMB). The **Objectives are also silent on the ethical obligations of the regulator** – the Drugs Controller General of India (DCGI) and CDSCO. Given that CHIS involves higher risks than conventional clinical/drug research does, for participants as well as for the public, the Statement **should specifically provide for greater involvement of participants and civil society in the onsite oversight** of **CHIS**.

	The Statement proposes CHIS for infections which are self-limiting and/or for which effective treatments are available. It must also be stated that CHIS is often conducted for those infection whose infective pathogens are not amenable to animal studies.
Section 3 - General Considerations. **2.1 Challenge Stains** 2.1.1 of the Statement says "use of well characterized strains that have been previously used in similar studies is encouraged … the sequence of the strains 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 Statement says that "the development of challenge strains…. should be in compliance with current GMP and other regulations as applicable". 2.1.3 The Statement says that lab testing of strains is to be conducted in certified labs that have Biosafety level (BSL) 2 *or* higher standards of safety protocols. 2.1.4 and 2.1.5: The statement makes a brief mention of genetic modification for the development of challenge strains and requires approval by a Review Committee on Genetic Manipulation and a Genetic Engineering Appraisal Committee. **2.2 Study Design & methodology**	**General considerations is Section 2** **<u>2.1 Challenge Strains</u>** **2.1.1: of the Statement needs to explain why, if CHIS has already been conducted using certain strains, the same CHIS should be conducted in India, exposing participants to risks**. If the sequence of strains is known, is it not necessary to deposit them with a known and authentic depository prior to conducting experiments? Lastly, the Central lab is not named, nor the standards to be maintained and complied with, nor the mechanism for surveillance so that these standards are not violated. 2.1.2: The GMP standards currently in force were not formulated for use on challenge strains, and they are not adequate for it. The Statement ought to specify that **CHIS may not be allowed in India until GMP standards specific for challenge strains are formulated here.** 2.1.3: BSL-2 level standards will be too low for challenge strains. **The Statement should specify that the standard to be used for CHIM should be *<u>BSL-3 or 4 or higher</u>*** depending on the safety risk of the pathogens concerned. 2.1.4 & 2.1.5: The Statement needs to provide some examples of the safe use of genetically engineered challenge strains and the additional safety measures necessitated for CHIS. Regarding the use of genetically engineered challenge strains, the **Statement must provide clear reasoning and identify diseases for which such strains will be needed**. The complete impact of the use of such strains is uncertain and unknown and it is difficult to predict the full effects on participants of these studies as well as on future generations. ***Given the seriousness of genetic modification of an organism to use for producing infection, a separate section with complete details of safety requirements must be created in the Statement.*** **<u>2.2 Study design and methodology</u>** The Statement does not provide any criteria for assessing whether a particular CHIS on a disease is essential for our

	country. It **needs to explain what additional social value the CHIS will provide by deliberately infecting participants when such infection is routinely happening naturally in the community at a high level, making it easy to study**.
The Statement says that CHIS will be conducted for **t**hose infections which are self-limiting or for which treatments are available.	This statement of CHIS to be conducted for self-limiting infections, or where treatments are available needs to be more specific as there are self-limiting and untreatable infections which can result serious residual injuries, or even death, i.e., Zika virus, SARS COV2. **It is also necessary to qualify the statement on availability of treatments, as there are infections for which there may be treatments, but they may not fully cure a person.**
2.2.1: The Statement states that "scientific requirements are unique to each disease, and the study design should be specific to each disease."	2.2.1: This needs to be explained in lay language. **What are the different designs used in the history of CHIS, and what were the different issues for protection of participants and safety to the public posed in each one**? Are there different scientific standards, laboratory quality standards and site standards and ethics requirements for each design?
2.2.2 The Statement states that "justification and supporting peer reviewed literature should be considered when determining sample size."	2.2.2: This is a scientific issue. For conventional clinical trials, there is a specific method for sample size calculation. Is there a different but specific method for CHIS? The Statement seems to suggest that CHIS enables production of evidence as good as in conventional trials, with a smaller sample size. So, **the method for sample size in CHIS needs explanation.**
2.2.3: CHIS specifically recruits healthy participants.	2.2.3: **But the statement does not define the criteria for identifying healthy participants.** Will it be done as per an operational definition requiring screening for a select few diseases or will it be broader warranting certain mandatory tests?
2.2.5: Methodology should outline steps, etc.	2.2.5: Different procedures followed for inoculation will warrant different steps for protection and welfare of participants. **These steps should be listed along with the procedures.**
2.2.7 states that "The interpretation of the results should take into account the unique methodology, potential and cofounding factors and limitations of the study."	**2.2.7: The additional limitations of the specific CHIS conducted should be mentioned.**
Section 4 - Responsible conduct of Research	**<u>Section 3– Responsible Conduct of Research</u>** **There is conflicting and contradicting guidance in the Statement, and there is no clarity on what is necessary**

	and what is not. No definitions have been provided in the Statement, rendering the entire guidance vague and arbitrary.
3.1 Institutional requirements 3.1.1: The Statement says "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. … should be duly equipped with the required budget, space, and infrastructure required for CHIS."	**<u>3.1 Institutional requirements</u>** 3.1.1: This is vague and permits multiple interpretations. It is not clear if the terms "centre" and "institution" are the same. How long is "extensive"? What types of clinical trials should these centres be experienced conducting? What specific facilities should be in place? Many so-called tertiary facilities in India lack some vital facilities. What equipment, space and infrastructure, and expert human resources are needed? **The statement should give specific physical, medical, expert human resource and process standards.**
3.1.2: CHIS will be conducted in closed settings, etc.	3.1.2: **needs to provide specific criteria for calling a CHIS site a "closed setting",** with standards aligned with any emergency and critical care requirement of participants and prevention of spread of infection by the challenge strain used (more so if it is genetically modified and likely to mutate).
3.1.3: requires institutions to comply with the standards of CDSCO and BSMC.	3.1.3: The **current standards of the CDSCO for GMP and Good Clinical Practice do not mention CHIS**.
3.1.4 mentions accreditation of laboratories, site/institution, IEC, etc.	3.1.4: But **none of these accreditation bodies in India has specific standards for CHIS**.
3.1.5: Regular internal audits, etc.	3.1.5: For CHIS, internal audit is not sufficient to maintain the high standards for patient safety, safety of research staff, and the community. The **statement should give details of the external audit process by the national clinical trial regulator.**
3.2 Responsibility of Researcher The Statement states that "the researcher and their team should be adequately qualified, trained, and skilled with prior experience in conducting clinical trials."	**<u>3.2 Responsibility of Researcher</u>** **The Statement should specify the level of qualification, training, skill and minimum number of years of experience in doing CHIS.** There is no agency to identify protocol violations and neglect in duty to participants in clinical trials, and there is no provision for sanctions or punishments for researchers/institutions/sponsors who violate law and ethics. Given the seriousness of CHIS, **the Statement must establish processes to make violators face consequences.** Moreover, the IEC is not required to hear the voices of participants, and participants and patients are not provided

	with any agency. Given the seriousness of CHIS, **the Statement must establish processes to give a voice to participants.**
3.3 Collaboration & data sharing The Statement acknowledges that CHIS is a highly complex research enterprise and therefore there is a need for collaboration among researchers, institutions, and countries. In 3.3.1this is described as an opportunity for Indian researchers to learn to conduct CHIS.	**<u>3.3 Collaboration and data sharing</u>** On Collaboration & 3.3.1: In fact, this will be a collaboration between unequal –the foreign expert backed by the money of sponsors and the Indian non-expert who cannot do CHIS without the former -- with many ethical problems. This section must address the following concerns: Who will decide the priority for conducting CHIS? The statement must **provide clearly what the social value will be of a particular CHIS for India.** The articulation of social value as a principle of research ethics as applicable to India is critical. In the past, unequal collaboration has caused "ethics dumping" and "double standard of ethics", leading to exploitation and harm to participants in LMICs. **The Statement does not show any evidence that it incorporates the highest international ethics standards for prevention of exploitation and harm to participants**. The Statement must make **strong provision for access to drugs and vaccines that are developed by conducting CHIS in India to participants in future and also to Indian people at a cost that the country and underprivileged people can afford.**
3.3.2: All parties to collaborate throughout the study	In 3.3.2: Sponsors and funders of the development of new drugs and vaccines are often pharmaceutical companies who benefit from trials, including CHIS. They have a strong conflict of interest and need to be kept at arm's length. However, 3.3.2 wants funders of CHIS to be involved throughout. There is no reasoning provided for it and **the perils of close involvement of sponsors/funders are not taken into consideration. If such a thing is done, the Statement must provide safeguards and firewalls**.
3.3.3: Collaborative partnerships, MOUS, etc.	**In 3.3.3 International collaborations for CHIS must be based on legally enforceable clinical trial agreements and not on memorandums of understanding.** These agreements must contain details about who will pay for injuries, deaths, ancillary care, violations of ethics and laws, and harm caused to research staff, communities, and the public in case of infection with the challenge strain spreading, and so on. They should also have commitment and budgets for local capacity enhancement and ought to give equal status to local researchers.

3.3.4 **states that CHIS may use sensitive personal data to create harmful biological agents or conduct potentially harmful experiments.**	3.3.4: This statement needs detailed explanation.
3.3.5 allows "preference" to researchers/sponsors for sharing anonymized raw data in the public domain.	3.3.5: It should not allow such a preference but state clearly that any raw data where confidentiality aspects are adequately taken care of cannot be allowed to be treated as trade secret or intellectual property of researchers and companies. The data are of the participants and communities who made research possible, and they can't become ownership of a few. Therefore, **all anonymized data of CHIS should be made available in the public domain.** Legal standards for data protection in terms of privacy and confidentiality are greater in high income countries than in India. So, **these higher standards for data protection** must be followed in collaborations.
3.3.6 Publication of results	3.3.6 The provisions made for publication are inadequate. **Publication of *all* results of CHIS should be required** – including of failed CHIS, and negative results -- and the publication must include a clear estimation of adverse events and harms.
3.4 Scientific Approval 3.4.1 to 3.4.3: Robust scientific review, peer review, appropriate body.	**<u>3.4 Scientific Approval</u>** 3.4.1-3.4.3: CHIS studies are normally done for infections with their medical consequences, both of which are known. CHIS is not a new method of doing research and like any other research, it studies disease for which a certain level of information is already available. Therefore, **a knowledge threshold should be described for doing CHIS** so that healthy participants are not exposed to something for which the researchers do not have adequate knowledge. Scientific reviews for research protocols are generally specific to the disease and medical condition. The Statement should **describe the specific expertise needed for a given CHIS protocol**, in addition to the general expertise and robust review that ought to be present in any scientific review.
3.4.4: Conflict of Interest	3.4.4: For Conflicts of Interest of the scientific committee, its members and the institutions, the mere declaration COI itself is not management. The Statement **must describe the different kinds of management of CoI and how each one is applied**.
Table 1: Examples of disease-specific considerations	**Table 1 eliciting examples of disease-specific considerations needs to be completed**. It also needs to

	provide guidance on what ought to be done for each disease-specific consideration.
Section 5 – Ethical Considerations Specific to CHIS	**<u>Section 5 – Ethical Considerations Specific to CHIS</u>** The opening paragraph of this section must categorically state that **the most important ethical consideration in CHIS is harm-benefit, and it is privileged or held above the consideration of participants' consent**. This general principle is all the more important in CHIS which deliberately infects individuals, causing harm, howsoever reversible it may be. At a formal level, CHIS goes counter to the medical dictum of "first, do no harm."
5.1 Deliberate infection	**5.1 – Deliberate infection** The terms **"Deliberate infection" and "Deliberate harm" must be defined and the conceptual difference between the two explained.** The "Deliberate harm" in Phase I clinical trials may be different from that in CHIS. The notion of a "permissible" level of harm, how the limit would be set, and by whom needs to be stated. The possibility of long-term harm in CHIS -- the need for monitoring for this, and how this would be factored in for compensation – must be stated.
5.1.1 and 5.1.2 state that information needs to be provided to the participants, who should be made aware of the risk mitigation plan in place.	5.1.1 – 5.1.2: The statement must **specify the assessment of the level of potential deliberate harm, the reversibility of this harm, and the provisions for minimization and mitigation of harm.** However, it must be noted that provision of such information in the consent process is not the main way for tackling problems associated with deliberate infection or harm, even when relatively low-risk infections are taken up for CHIS. **The well-being of a person takes precedence over principles like autonomy in the research setting.** Finally, the statement must explain how CHIS can take place when laws like the Madras Public Health (Amendment) Act 1958 state that any act performed with a deliberate intention to cause an infection is illegal. **A CHIS may be in direct contravention of such an Act.**
5.2 Selection of Participants 5.2.1: Adult healthy participants	**<u>5.2 – Selection of Participants</u>** 5.2.1: should **specify what a rigorous screening** of health status of participants would consist of in order to declare a person healthy.
5.2.2 describes altruism as a genuine desire to contribute to public health advancement.	5.2.2: Assessment of altruism is an issue of contention even in conventional clinical trials**. The statement must provide a clear operational definition of "altruism" with criteria for its identification in participants,** and conditions needed

	to ensure that till the end of the research, the participation remains altruistic.
5.2.3: states that the participants should "preferably" be graduates.	5.2.3: This should be *required*, not preferable, and **participants must have at minimum a graduate level education**. In addition, participants' decision to participate in a trial is determined not only by the higher comprehension possible because of education, but also by their socio-economic condition resulting from their location, language, caste, religion, and other socioeconomic characteristics; those with bad conditions suffer from what is called "structural coercion". The Statement should take this into consideration and formulate guidance accordingly. **There should be unambiguous guidance that prisoners will not be recruited for participation.** It should also be stated clearly that participants must not be instructed to participate by their organization or by an employer or senior/superior officer. Moreover, the ability to obtain informed consent is not determined only by the level of education of the participant alone, but also by the simplicity, honesty, and completeness of the document and the way it is explained. This fact must be included in the Statement.
5.2.4 says while vulnerable groups are excluded from CHIS for now, this ban may be lifted in the future as Indian researchers develop the "capacity and experience" to conduct CHIS on these groups.	5.2.4: Vulnerability is overcome only by removing the vulnerability of the person/group, not by increasing the experience of researchers. ***The option to consider inclusion of vulnerable groups at a later point in time should be deleted from this statement.***
5.2.5 speaks of excluding people with pre-existing medical conditions from the study.	5.2.5: This statement does not make sense as only healthy participants may be considered for CHIS, and ***it should be deleted.***
5.2.6 says that studies should not be conducted on children "at present" but may be included at a later point "when deemed appropriate."	***5.2.6: This option of including children must be removed from the statement.***
5.3 Benefits and Risks The benefits *to participants* are listed before risks, and it is stated that the risks to the participants may or may not be significant.	**<u>5.3</u> <u>Benefits and risks</u>** This contradicts statements made earlier and in clause 5.3.3 that for CHIS the risks are uncertain.

5.3.1: Altruistic contribution to science 5.3.2 describes "laboratory investigations, ancillary care, counselling or other medical care" as indirect benefits. 5.3.4 mentions "expected symptoms", "risks", and "adverse events", and 5.7.1 adds the term "unexpected symptoms"	5.3.1: wrongly describes the "opportunity to altruistically contribute to science" as a direct individual benefit, which is not correct, and ***this point must be deleted*.** 5.3.2: Medical care is not a benefit for participants in CHIS who are healthy individuals, and ***this point must be deleted***. 5.3.4 and 5.7.1: The Statement argues for the differentiation between these terms without clear explanation. "**Expected/unexpected symptoms" and "adverse events" all follow from the deliberate infection of healthy participants and must be considered as important and serious as other adverse events *due* to the intervention and deserve compensation.** Even in the second stage of CHIS, no differentiation is required between adverse events caused by the drug/vaccine and those caused by the disease, as both are deliberate experimental interventions. Relatedness of an adverse event may be assessed only for scientific purposes. **All adverse events are reactions to the intervention and eligible for compensation.** Furthermore, the **current law on compensation** in clinical trials does not take into consideration this uniqueness of adverse events in CHIS and **will need an amendment if CHIS is done in India.**
5.3.5 to 5.3.8 list the problems that participants or the community may face due to CHIS, such as depression and isolation of the participant, as well as cross-infections, contamination and spread of the disease by the challenge strain in the community and the environment.	5.3.5 to 5.3.8: The Statement must **spell out the precautions that need to be taken to mitigate and control the spread of the disease**, and the action to be taken if such untoward incidents occur, whether due to inadequate safety standards, or errors, negligence, or misconduct on the part of researchers, the research team, or the research institute, etc. It must also state how such harm will be compensated.
5.4 Additional Safeguards 5.4.1 assures participants "healthy meals" and "basic hygiene such as clean water."	**<u>5.4 Additional Safeguards</u>** 5.4.1: A "healthy meal" can be vegetarian as well as "non-vegetarian' but given the cultural background of a bulk of researchers, the healthy meal may include only the former, i.e., vegetarian food. The Statement must clearly state **that participants must get healthy and adequate meals according to their cultural dietary preferences.** It should also require the provision of the **highest standards of hygiene, water, and sanitation.**

5.4.2: This mentions facilities for isolated and hospitalized CHIS participants to communicate with their families and friends. It also states that participants will get counselling for mental health and access to mental health professionals.	5.4.2: The statement should also specify the conditions in which participants will be ambulatory and allowed to live in the community for the duration of the study. In the criteria for staff in the CHIS, there should be a provision for a trained counsellor and availability of a mental health professional as a consultant.
5.4.4 to 5.4.6 state that all health personnel involved will be trained in infection control and provided with protective equipment. However, family members who visit the facility will only be tested and screened to prevent the spread of infection.	5.4.4 to 5.4.6: **The statement should require visitors to be provided with the same infection control training and facilities/equipment as health personnel get.** More detailed guidance is needed on the prevention/spread of infection from participants and protection of community and healthcare workers and other patients in the institution.
5.5 Informed Consent Introductory para	**<u>5.5 Informed Consent</u>** The Statement has laid down additional procedures for comprehension levels of trial participants, but it also needs to provide a **method for assessing investigators and staff's comprehension** of the protocol, the procedures for CHIS, the necessary safety measures, and the need for sensitivity toward participants.
5.5.1 speaks of written informed consent and audio-visual recording "when applicable", with requirements varying depending on "local regulations, institutional policies, and the nature of the study or procedure".	5.5.1: This must be **uniform, not varying, and consent taken only in the presence of an outside witness**. The protocol for AV recording for CHIS should be such that it captures provision of full and complete information on the researcher's part, and comprehension, genuine altruism, and voluntariness on the part of the participant.
5.5.2: The section on comprehension testing	5.5.2: The section on comprehension testing needs to **state how the capacity or competence to consent will be assessed**.
5.5.5: states that participants "will receive a **standard of care as appropriate** for the disease under study"	5.5.5: Standard of care as appropriate has been stated without specifying what is meant by "appropriate". This should be re-worded. **The principle of CHIS where participants are deliberately infected demands that they get the highest international standard of care**.
5.5.6 and 5.5.7 require an **assessment of altruism, voluntariness and absence of inducement**	5.5.6 to 5.5.7: Assessment of altruism, voluntariness, absence of inducement needs to be spelled out on how this assessment will be made.

5.5.9: states that the exact amount of payment to be made to a participant must be revealed only after s/he consents to participate.	5.5.9: This indicates that these **payments are potential inducement to participate**. Participants once they have consented will be compelled not to withdraw from a CHIS, vitiating the consent process. Furthermore, once information on payment is in the public domain, it is bound to serve as an inducement to other potential participants.
Table 2	**Table 2 needs scrutiny and drafting** to provide guidance.
5.6 Privacy & confidentiality 5.6.1 to 5.6.3: Data privacy, storage, data to be published	**5.6 Privacy and Confidentiality** 5.6.1 to 5.6.3: Privacy and confidentiality are fundamental rights that need to be protected, and no personal, identifiable information about the participants should be revealed to any third person without consent. Under the current ICMR guidelines, access to identifiable data is not only to the researcher, but also to the IEC and regulator. The measures of privacy protection must apply to all such parties too. The clause on confidentiality and privacy should also lay down the limited circumstances when confidentiality can be breached, and the steps that need to be taken for the same. The clause on confidentiality must also state **how the data, documents, videos, etc. will be kept safe and secure**, and how unauthorized access or use will be prevented. The clause on confidentiality must also include the **consequences for violation** of the clause, and the compensation that will be paid to the participant for this breach.
5.7 Payment for participation	**5.7 Payment for Participation** **The Statement fails to take a principled stand of no undue inducement**. There is a contradiction between the statements on undue inducement and a method of making payment without influencing the decision to participate. Besides, it may nullify the requirement of altruism.
5.7.1 & 5.7.2 identify two elements in payments: (a) reimbursement of expenses, inconvenience, and (b) severity of harm (the amount of payment being based on the degree of inconvenience and severity of harm).	5.7.1 & 5.7.2: This needs to specifically include **compensation for uncontrolled disease, side-effects, long-term and medium-term consequences**, and the potential of serious adverse or adverse consequences ranging from drug resistance to a reinfection with severe form of the disease.
5.7.3 & 5.7.4 propose that "An additional payment may be made for participation, which could be	**5.7.3 & 5.7.4: The nature of this additional payment suggests that it will serve as an undue inducement**. These clauses are vague and leave scope for corruption.

in cash or kind." **5.8 Monitoring & Follow-up of Participants** 5.8.1 to 5.8.6: Monitoring & Follow up 5.8.6: The clause envisages monitoring of CHIS by the researchers themselves, ECs, sponsors, and regulatory bodies, with an option for independent monitoring. **5.9 Compensation for research-related harm** Introductory para: This section refers to the NDCT Rules, 2019, and the ICMR guidelines and states that compensation payable for CHIS would be guided by these two documents.	**<u>5.8 Monitoring and Follow-up of participants</u>** Clauses 5.8.1 to 5.8.6 conflate issues relating to monitoring of the Study and follow-up of participants. The two should be separated out. The Statement should **specify monitoring requirements for CHIS.** 5.8.6: It should **require that an external committee comprising community members, medical persons, etc. will do external audits at short intervals**, and at least once during the CHIS trial. Drug trials require a safety plan in place, with full information on how to identify and characterize adverse events and how to do their medical management, monitored by the PI at the site. The plan includes information on when to stop the trial, which is a decision taken by PI in consultation with the DSMB. In addition, the DSMB is an external monitor, away from the trial site, and evaluates adverse events and decides on continuation/stoppage/modification in consent, etc. A third element, an **onsite external monitoring committee specifically for CHIS,** should be considered. This could be a community monitoring committee with specified membership and powers. Regarding follow-up of participants (which should be a separate point), the statement **needs to present a short, medium, and long-term follow up plan**, covering psychological support, physical and mental health check-ups, with compensation not only for the visits in follow-up, but also if any untoward incident, spread of disease, etc. takes place post-trial. **<u>5.9 Compensation for research-related harm</u>** Introductory para: Reference to NDCT Rules 2019, & ICMR guidelines, 2017 for compensation - However, in **CHIS trials the harm is deliberate, and the same is not covered in either of the documents** referred to by this section. Further, the current **compensation formula for drug trials is inadequate for injury/death compensation in CHIS.** In clinical trials emphasis is given on determining whether an adverse event that caused injury or death was "related" to the experimental intervention/drug/vaccine. Thus, the task in therapeutic trials is to separate injury and deaths that could have been caused by the disease from those caused by the intervention. The latter adverse events are renamed Adverse

	Reactions and are eligible for compensation under Indian law.
5.9.3 Causality assessment	In CHIS, the disease itself is an experiment and in addition, there is testing of a drug or vaccine. Thus, the adverse event is *ipso facto* also an adverse reaction. So, **<u>any adverse event in CHIS that causes injury or death ought to be eligible for compensation without any assessment of relatedness.</u>** This must be clearly stated in the guidelines. ***Hence, clause 5.9.3 should be deleted completely.***
5.9.1 and 5.9.2: Insurance, corpus funds, etc. in budget	5.9.1 & 5.9.2: that state that insurance, corpus funds, etc. need to be envisaged and budgeted for, the costs of CHIS include not just the duration of the trial, but also short, medium, and long-term costs. The statement should spell out **how** the quantum of compensation will be calculated for patients, families, hospital staff and the community who may be exposed to the pathogens being tried in CHIS, and **who** will be responsible for payment of this compensation.
5.10 Post study access/ benefits sharing-opening statement 5.10.1 to 5.10.2: Access to direct & indirect benefits, information on royalties, etc.	**<u>5.10 Post study access/ benefit sharing-opening statement</u>** The statements in clauses 5.10.1 to 5.10.2 are vague – too general – without making any clear commitment for post study access. As stated by us earlier, there should be an **unambiguous commitment that all participants will receive, free, the drugs and vaccines developed from the CHIS they participate in, and people of the country will have access to them at the cost they can afford.** **Post study follow-up, the health of participants in CHIS needs to be monitored closely**, and they should be regularly provided information on the development of the drug/ vaccine that was tested on them, as well as information relating to the disease. They should be involved in analysis, assessments, etc. of CHIS.
Section 6 – Ethics Committee Considerations The Statement in this part refers to the ICMR 2017 guidelines, with some additional provisions, and also lays down details on what members of the committee should review.	**<u>6. Ethics Committee Considerations</u>** **The following issues need to be addressed with respect to clause 6:** 1. A rationale must be given for restricting the number of experts for further opinion to 1 or 2. 2. There must be clarity on whether these experts will be from India or abroad. 3. There must be guidance to show how the experts will be identified, what their experience or qualifications should be, how their track record will be checked, and who will check it, prior to taking their expert opinion.

	4. There must be clarity on how the risk-benefit analysis will be conducted for CHIS. 5. There must be guidance to the EC/ IRB on understanding the consequences of CHIS, on how participants will be recruited, and the type of checking, caution, and monitoring they are required to do if CHIS is allowed in their institute. 6. There must be guidance to the EC/IRB to check the facilities, infrastructure, availability of protective gear, etc. of the CHIS site, the labs, etc., and to check who has access to these sites, and how often people are allowed in these sites where CHIS is taking place. 7. There must be guidance in the Statement on how the EC/ IRB are to monitor CHIS trials, whether they may allow deferred recruitment, whether they must monitor the site after recruitment of the first participant, before allowing recruitment of the second, and so forth. 8. There must be guidance on how the EC/ IRB can intervene in case there is a leakage or an untoward incident, and what immediate action they need to take, or direct the researcher, institute, and/ or Sponsor to take when things go wrong, or there are major adverse events or serious adverse events. 9. There must be guidance to the EC/ IRB on how they should involve the participants in determining compensation for CHIS 10. There must be guidance to the EC/IRB as to when they should stop the trial, what action they should expect or direct in case the participant withdraws, what action they should take in case there are short, medium, and long-term consequences on the health of the participant. 11. There must be guidance to the EC/IRB on how they should encourage complaints or grievances to be filed with them by anyone involved in CHIS – whether participant, staff, researcher, etc., and how these complaints should be addressed in a just and equitable manner.
6.1.1 to 6.1.6: Roles and responsibilities	6.1.1 to 6.1.6: are just reiteration of the 2017 ICMR guidelines.
6.2 Ethics Review	**6.2: on Ethics Review** needs to provide guidance on the substantial issues to be reviewed; at present, it only lays down procedures.
Table 3	**Table** 3 is a framework to guide ethics review and **needs to be drafted to provide clear guidance** on the issues discussed in this comment.
6.2.1 to 6.2.13	Statements in **clauses 6.2.1 to 6.2.13 need to be modified to remove contradictory, conflicting, vague, ambiguous,**

	and arbitrary statements. (a) The statements acknowledge conflicts of commercial interests which is contrary to permitting payment for participation which gives an impression of purchase of participation. (b) There is a reference to public engagement to build trust but there is no methodology given for such engagement. (c) It states that participants should not be exposed to unnecessary risks and potential harm should be minimized though risks and harm are intrinsic to CHIS. (d) A robust system of review is called for, but the meaning of 'robust' is not defined, etc. 6.2.9: states that a sub-committee comprising two or more members who possess knowledge and expertise to review SAE of CHIS should be included but it does not specify the level of knowledge and expertise required. The Statement should **require that members of the community and participants be made part of the AE/ SAE assessment in CHIS**. 6.2.10: on DSMB does not state that the **DSMB for CHIS should be an independent body and ought not to consist of members who are paid by the Sponsor, institute or researchers involved, nor should it contain members of the EC/ IRB** who are approving the protocol. 6.2.12: envisages a common review of multicentric CHIS, indicating that multi-country trials may also be envisaged for CHIS. This **requires a detailed explanation of why such trials might be necessary; the implications of allowing multicentric CHIS**; who will ensure that all the centres are at par in terms of infrastructural facilities for conducting CHIS; the increased risks, in a multicentric CHIS, of exposure to more persons and more communities, etc. As noted earlier, the CHIS is done in two stages – development of disease model and then testing of drug/vaccine. The **ethics approval therefore needs to be in two stages** so that only after assessing the possibility of harm in developing disease model, the decision to permit drug/vaccine trial is taken.
Section 7 – Advocacy, Public Engagement and Public Trust **7.1 to 7.3, including 7.3.1 to 7.3.9**	**<u>Advocacy, public engagement, and public trust</u>** This section requires clarity on a few issues. It must state **where the participants be recruited from**; it must also state **who should NOT be recruited at all**, which is important to prevent vulnerable participants, whether they are staff, students, or healthy attendants of patients in the hospital or

	institute, etc. Public trust must be based on the provision of correct and honest information on CHIS and the risks involved for the participants. The objective of public engagement is to create deliberation with the public so that the public is not used in an instrumentalist way to merely recruit participants from them; public engagement must encourage community oversight of CHIS and participation in decision making on compensation and other processes. Public engagement is also needed to prepare and train the community to take safety measures in the case of the spread of infection with the challenge strains of pathogens. The fear among people of a research method that deliberately infects participants is real, and it is not only because of their misconceptions about CHIS. The fear is also because of their distrust of researchers, institutions, and regulators; all of these have lost credibility in various degrees because of their elitism, and their insensitivity to people. To regain trust, simply bombardment with the "correct" information using public communication professionals will not be sufficient; in fact, such attempts may increase the public's distrust. What is needed is genuine deliberation and opening clinical trials in general and CHIS in particular to public participation and systematic monitoring.
Table 4	**Table 4 does not explain anything and must be redrafted.**
Section 8 – Research Governance and Other Considerations **8.1 to 8.7**	**<u>Research Governance and other considerations</u>** 8.1 to 8.7: appear to lower standards, where higher legal and ethical standards are required for CHIS.
8.1: The Statement in clause 8.1 requires compliance with GMP, the News Drugs and Clinical Trials Rules, 2019, etc.	8.1: However, **it is not clear if GMP covers manufacturing pathogens and strains to be used in experiments**. Further, the **NDCT, 2019, was not drafted with CHIS in mind** and does not include any provisions, infrastructure, consenting processes, etc. relating to CHIS.
8.2 to 8.3: Laboratories need to be accredited.	8.2 and 8.3: However, the biosafety levels necessary for all kinds of pathogens, without classifying them as per their infectiousness, have been stated as BSL2 or BSL3 levels. It is **necessary to require the highest BSL levels and to specify these in the document**.
8.4 to 8.5 refer to other guidelines	8.4 to 8.5: Other guidelines - but it is not **clear if those guidelines contain any provisions relating to CHIS**.
8.6 to 8.7: International collaboration approvals	8.6 to 8.7: It is not clear from clauses 8.6 to 8.7 from which authority international collaboration approvals are required,

	as two authorities have been cited, and a third is the CDSCO, and other authorities that review genetic manipulation and genetic engineering.
Annexure A- Public Engagement	We have explained above in section 7 that public must be provided with honest and full information about what exactly is done in the CHIS – that there is a deliberate infection and harm but the same is in controlled condition and treated, and welfare of participants will be top priority. And second that researcher/institute/sponsor must try to gain trust of public by opening the CHIS to public participation and scrutiny.
Annexure B -Informed Consent	Please see our comment on the section on informed consent above. The annexure on Informed consent does not mention what CHIS is about, what are the steps and stages in CHIS, there is no mention of "deliberate harm" or "deliberately infecting" the participant. The comments mentioned in part 5 above & other portions relevant to these aspects are reiterated here.
Annexure C - Test of Understanding	Testing of Understanding of the Participants by means of quizzes, discussions, tests, etc. are not the only methods of assessing understanding. Such methods should be video recorded, and must be reviewed by an independent committee prior to any intervention on the participant. Further, Informed Consent should not be a one-time process, but should be a continuous process with every intervention and follow up with the participant. Participant's understanding is dependent on how the matter has been explained to her/him, in a simple, honest manner, in a language that the participant understands. Full information is required, that include all the risks that may occur in the short, medium and long-term on the participant in case they enter the trial. Assessment needs to be done also of the Researcher and the research team on their understanding of the protocol, procedures, methods, and how they are supposed to manage AEs/ SAEs, or any untoward incident during the trial.

A general comment on Annexure: As we have argued above, the most important principle to deal with in the CHIS is Harm-Benefit, and in that specifically harm-benefits related to the target disease infection and the testing for the drug/vaccine for the same. It would be good to explain the specific methodology for the assessment of the Harm-Benefit by researchers and IEC members in a separate annexure.

Conclusion

Open discussions must be responsive to the concerns and expectations of the people of the country, particularly the marginalized that are most likely to be affected by these promised innovations. Any proposed guidelines/ statements, and policies must provide opportunities for all people to influence public deliberations about CHIMS & CHIS, as well as ensure that the public is actively involved in these discussions and debates and that a broad range of public voices is represented.

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