

CLINICAL TRIALS POLICY

Clinical trials constitute an essential step in translating biomedical advances into healthcare improvements. Well-designed and scientifically rigorous randomized clinical trials are the gold standard for the assessment of safety and efficacy of new vaccines to prevent death and illness. CEPI supports clinical trials as a key part of our vision where vaccines can prevent outbreaks of emerging infectious disease from becoming humanitarian crises.

This policy sets out:

- the overall requirements of the awardee (or potential awardee)
- the overall guidance for the clinical trials funded by CEPI
- ethical principles that underlie CEPI’s funding decisions on research projects
- some of the main requirements for clinical trial set-up/conduct/reporting

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1. Overall requirements of awardee

Sponsorship

All trials are required to have a sponsor(s) who is qualified to assume the responsibilities and accountabilities associated with this role as per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP), which defines 'sponsor' as "an individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of clinical trial". CEPI expects awardees to act as the designated sponsor of the clinical trials and to take responsibility for the initiation, management, oversight, and communications with regulatory authorities on the trial. CEPI must be informed in advance of any proposed changes to the sponsorship arrangements.

The sponsor must have in place or implement prior to any clinical trial activity a system to manage quality throughout all stages of the trial process. Written SOPs must be available to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s). If contract research organizations (CROs) are used to execute the trial, the sponsor will maintain overall responsibility and has to ensure adequate trial oversight.

ICH-GCP and Ethics Training and Knowledge

All CEPI-funded clinical researchers must have an understanding appropriate to their role of the ethics of research involving human participants. All CEPI-funded clinical researchers need to ensure a recent and documented ICH-GCP training and training in relevant ethics guidelines prior to any study activity, as outlined in section 3.

Reports

CEPI requires awardees to share a synopsis of clinical trial results as close to real time as possible and within 12 months of the last subject last visit (LSLV) for adult and no later than 6 months after the LSLV for paediatric studies. CEPI has committed to implement the requirements set out in the May 2017 joint statement published by WHO on clinical trials reporting (<http://www.who.int/ictrp/results/jointstatement/en/>). In addition, CEPI funded trials must share the notes from the DSMB meetings and any IRB /ethical review outcome reports with the CEPI Secretariat. In the event of a public health emergency (as defined by public health officials) caused by the pathogens for which CEPI funds vaccine development, CEPI expects that awardees who have product related information with immediate implications for public health will share this with CEPI and the WHO.

2. Overall guidance for clinical trials funded by CEPI

CEPI's objective is to support high quality trials that are well designed and well executed'

The principles of ICH-GCP should apply for all clinical trials funded by CEPI to ensure that:

- The rights, safety, integrity and confidentiality of trial subjects are protected, and
- Data and reported results are valid.

CEPI-supported clinical trials should not interfere with any standard of care in the country where the clinical trial is executed.

The data should be managed and shared in a way that maximizes benefits to human health.

The clinical trials should be undertaken in accordance with GCP, national regulations and appropriate local standards. Research conducted during an infectious disease outbreak should be designed and implemented in such a way that it does not interfere with other public health interventions, and adhere to locally accepted norms and standards and adopt learnings from recent outbreaks.

Protocols should be developed in accordance with ICH-GCP requirements. Specifically, the clinical trial protocol should include a benefit risk assessment and should specify how the planned research will provide benefits on a societal, group or individual level.

Research funded by CEPI and involving human participants should:

- have outcomes that should lead to health benefits with applicability to the target populations/ regions;
- be research that could have a 'global public benefit'
- not compromise the public health response to an outbreak or the provision of appropriate clinical care,
- have the sponsor of the trial outline the potential benefits for the community or individuals as part of the study implementation

Approvals

CEPI requires awardees to have all relevant regulatory and ethical approvals, and appropriate governance mechanisms in place before the clinical trial is initiated. Applications for funding may be made before such approvals are in place. However, in the event of an award being made, commencement of the clinical trial cannot be initiated until all approvals and governance mechanisms are in place.

Approval documents must be made available to CEPI upon request at any point during the lifetime of the CEPI-funded project, including the retention period. Approval documents must be retained for at least 10 years or according to local regulations, whichever is the longest.

3. Ethical principles

Expectations and standards

The ethical acceptability and scientific validity of CEPI funded research are of utmost importance and we expect best practice ethical and scientific standards to be maintained throughout the lifetime of the funded projects.

Research involving human participants is governed by numerous national and international guidelines. The Declaration of Helsinki by The World Medical Association, the International Ethical Guidelines for Biomedical Research Involving Human Subjects published by the Council for International Organizations of Medical Sciences (CIOMS), and the Nuremberg Code are some of the most important guidelines in this regard and they set out requirements on the rights and safety of research participants and standards for research design and conduct.

The WHO's 2016 Guidance for Managing Ethical Issues in Infectious Disease Outbreaks provide guidance on embedding ethics into an alert and response system for epidemics and other public health emergencies and are thus of particular importance for CEPI funded projects. CEPI expects awardees to heed these considerations throughout the research.

Ethical review

Ethical review should be sought from an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) or equivalent that meets requirements set out by ICH-GCP. Such review must be undertaken in all countries where any part of the clinical trial is to take place. If no committee constituted according to ICH-GCP exists in the country where the clinical trial is being carried out, CEPI, in conjunction with local stakeholders and the awardee, will work to identify an appropriate path for such ethical review. The awardee is responsible for ensuring that the procedures and quality of the ethical review and that the composition of the ethics committees involved are formed and operated in compliance with ICH-GCP principles. CEPI requires the awardee to share confirmation of all ethical approvals if requested and funding will be conditional on such approvals. Requirements for ethical reviews and standards do not differ under emergency epidemic situations.

Community consultation

Community engagement is increasingly seen as a key element of ethically conducted research. Such engagement should be proportionate to the scale and impact of the study being undertaken.

Community consultation and engagement (including the involvement of local researchers) prior to, during and after the course of research, particularly in low income countries, is essential to build and maintain trust. Building trust is of particular importance if the trial is occurring in an emergency outbreak situation where fear can dominate public perceptions and fair access to potentially effective interventions is in focus. We specifically refer to the 2016 WHO guidance on good participatory practices in trials of interventions against emerging pathogens.

4. Requirements for clinical trial set-up/conduct/reporting

The clinical trial results must meet the standards and the requirements of geographically relevant regulatory agencies (such as the FDA, EMA, Swissmedic, PMDA Japan, ANVISA Brazil, KFDA Korea, Health Canada and others) and be able to support licensure, stockpiling or emergency use and assessment listing (EUAL).

Regardless of where they are conducted, all clinical trials included in applications for marketing authorization for human medicines must have been carried out in accordance with ICH-GCP, the Declaration of Helsinki and local clinical research regulations. All CEPI funded studies should be scientifically valid and therefore quality management and monitoring are important. All studies should include a section on clinical quality management. Monitoring, data management, and statistical analysis plans are to be in place prior to study initiation and should reflect the risk and complexity of the study design and operational setting. The aim should be to ensure data quality and that the rights and safety of the participants are being protected. CEPI reserves the right to perform or contract independent audits of study, PI, sponsor, contract research organization (CRO), lab and other subcontractors.

Trial registration

CEPI requires all clinical trials to be registered with [ClinicalTrials.gov](https://clinicaltrials.gov), the [ISRCTN registry](https://www.isrctn.com), or another register listed on the WHO [International Clinical Trials Registry Platform \(ICTRP\)](https://www.who.int/clinical-trials-registry-platform) and for awardees to inform CEPI of such registrations with the trial ID when it is granted. Where possible, awardees should indicate that the trial has been funded by CEPI, citing the relevant grant or contract number. CEPI requires that clinical trial websites are regularly updated and results are posted as per requirement.

Inclusion and exclusion of research participants

Individuals must not be enrolled in a CEPI-funded clinical trial if this would:

- contravene relevant legislation;

- contravene relevant codes of conduct or guidelines, such as professional guidelines; or
- contradict the inclusion and exclusion criteria as defined in the approved protocol

In planning any clinical research, a careful benefit-risk assessment should always be carried out so that participants or communities are not exploited or disadvantaged by their inclusion in the research. The risk assessment should include a comparison of the degree of risk (if any) with the anticipated benefits of the research to the participants or communities involved.

Informed consent

Individual valid informed consent shall be obtained in accordance with ICH-GCP and local regulations. Consideration should be given to local literacy levels. When reviewing applications, CEPI may request clarification or information about the proposed consent procedures and forms.

Research involving vulnerable individuals and children

Subject to proper description in the protocol and relevant ethics committee approval, CEPI will consider funding clinical research involving individuals who may be at risk due to participation, are incapable of providing consent, including children, unconscious people and people with mental disabilities. This is only permitted as long as their participation is deemed necessary for answering the research question and all measures have been taken to safeguard and promote the interests of such subjects.

Awardees must carry out all necessary discussions with parents or other legal guardians and/or an appropriate responsible legal authority to ensure that such research complies with relevant regulations, best practice guidance and local regulations (e.g., determining whether one or both parents need to consent in the case of a paediatric patient). In situations where the participants may be unaccompanied, or the participants are unable to give their own consent CEPI will consider alternatives to the standard consent process. Any such alternative process should have been developed through careful community consultation, and where possible be based upon previously used approaches that have been approved and successful in similar situations. Ethics committees must approve any such approach and CEPI may seek external review.

It is important to note that the legal age of adulthood can differ between countries. If relevant, the protocol must provide guidance on a situation where the parents are minors. CEPI expects that such issues would be considered by ethics committees in approving research protocols.

Use of biological samples and data

Where research will involve the collection of blood samples, human tissue and/or data, awardees must outline as part of their application how these will be collected, stored and accessed by any third parties and ensure that appropriate ethical approvals and individual consents are sought. The confidentiality of research participants must be safeguarded, and data and tissues must always be shared in line with the purpose for which consent was given, and must respect national and international norms and legislation.

The consent process should, wherever practicable, include seeking consent for secondary use of the biological sample or data in subsequent clinical research studies. CEPI recognizes, however, that in some situations, this may not be possible. In such cases, we consider that it is acceptable to use samples and/or medical data for secondary purposes without returning to the participant for specific consent (a broad consent model), if the proposed research:

- has clear healthcare benefits;
- complies with relevant national laws;

- complies with any binding codes of practice or ethical guidance (such as professional guidelines or licensing regulations);
- is consistent with the consent as approved by an ethics committee for the original study
- is approved by the local ethics committee
- uses samples or data that have been anonymized (either fully or, at a minimum, 'de-identified');
- meets policy requirements regarding secondary use as required by the awardee's own normal standards and procedures; and
- includes appropriate governance/oversight mechanisms to monitor consent for the original study and any cases where it is withdrawn, where practicable.

Data privacy

Study participants need to be adequately informed of data privacy. As sample data generated during clinical research might be stored, processed and analyzed in a jurisdiction with less stringent criteria for maintaining data privacy as compared to the country where the clinical research is being conducted, study participants need to be informed of this as part of the consent process.

Insurance

For all trials, the sponsor is responsible for ensuring that appropriate insurance is in place. Insurance is to be maintained throughout the trial. CEPI reserves the right to see the relevant documents on request.

Audits

The awardee has to ensure that potential regulatory audits/inspections or sponsor audits are described in the protocol and patient information/informed consent forms. Furthermore, CEPI reserves the right to perform, at its own cost, pre-, during or post-study audits by professionally trained auditors. The awardee needs to ensure collaboration and data / site access for these auditors.

Transparency and publication of results

Trial results are to be posted on the clinical trial register sites in the format and at times according to the underlying regulations and as outlined in our data sharing policy. We support unrestricted access to the published outputs of research, and expect awardees to make their research findings freely available, including negative results. See also CEPI's policy on open access publications.

Collateral benefits

Collateral benefits may arise as a by-product of carrying out clinical research, whether or not they are necessary for the research design. Examples include the provision of healthcare benefits to communities during a project, strengthening local research capacity and providing research-related technical or clinical equipment. Thus, local clinics associated with a research project may benefit from improved diagnostic, medical and scientific expertise.

CEPI will consider supporting the provision of collateral benefits as part of a project, where they are not of such a degree that they could have an adverse effect on the local research environment or could create an undue influence to participate in research. The awardee must fully explain the nature and sustainability of any collateral benefits as part of the research proposal, and these must form part of the application and be approved by relevant ethics committees.

Where recompense for participating in research is offered, either financial or in kind, it should be set at an appropriate level to cover, for example, reasonable expenses and subsistence costs. Any recompensation or benefit must be approved by the IRB. Where it is proposed to offer healthcare unrelated to the specific research question, we recommend that this should generally be in accordance with the locally recommended best standard of care.

Health-related findings in research and feedback to participants

In the course of a study involving human participants, awardees may make a finding that has potential health or reproductive importance for a research participant. Potential health related findings include both findings that relate to the aims of the study (pertinent findings) and findings that are unrelated to the aims of the study (incidental or unsolicited findings). They do not include aggregated research findings that are not meaningful at an individual level.

We expect all awardees to carefully consider the issues around health related findings when establishing a study involving human participants. In particular, awardees must:

- have a policy indicating whether or not health related findings will be fed back to individuals that can be clearly articulated;
- be able to demonstrate the reasoning behind their policy to research participants, funders and the EC/IRB or equivalent;
- include clear information on the study policy on the feedback of health related findings in the consent process; and
- in cases where the policy is to provide individual feedback on health related findings, develop a practical feedback pathway that is adequately resourced.

All those seeking CEPI funding should consider their approach at the application stage. CEPI can require the awardee to share their approach to health-related findings with us during the lifetime of the project. We cannot provide any advice on particular health-related findings policies or approaches and we do not accept any responsibility for any matter arising out of any health-related findings policy.

Awardees must consider the circumstances and mechanisms by which aggregated or individual clinical research findings might be made available to research participants and their communities, where this is deemed appropriate, and the manner in which such information is presented. CEPI encourages and supports feedback to participants.

5. Summary of Essential Documents to be Provided to CEPI

The following essential documents should be made available to CEPI by the Awardee:

- Confirmation of sponsor arrangements
- Short overview of quality management system / list of SOPs
- Study protocol, informed consent form (ICF)
- Approvals from IEC/IRB and regulatory authorities
- Insurance statement
- Approach to health-related findings (on request)
- Confirmation of clinical trial registration
- Clinical Study Report Synopsis
- Quarterly status reports
- DSMB minutes
- Minutes of interactions with IRBs / NRAs

Other essential documents as set out by ICH-GCP should be made available to CEPI upon request.

6. References

- The Council for International Organizations of Medical Sciences in collaboration with the World Health Organization: 'International Ethical Guidelines for Biomedical Research Involving Human Subjects, 2016
- The Council for International Organizations of Medical Sciences in collaboration with the World Health Organization: 'International Ethical Guidelines for Biomedical Research Involving Human Subjects, 2002
- Council of Europe: 'Convention on Human Rights and Biomedicine', 1997
- Council of Europe: 'Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research,' 2005
- International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceuticals for Human Use: 'ICH Harmonized Tripartite Guideline. Guideline for Good Clinical Practice,' November 2016
- National Academies of Sciences, Engineering, and Medicine. 2017. Integrating Clinical Research into Epidemic Response: The Ebola Experience. Washington, DC: The National Academies Press. <https://doi.org/10.17226/24739>.
- United Nations Educational, Scientific and Cultural Organization: 'Universal Declaration on Bioethics and Human Rights,' 2006
- Wellcome Trust and the Medical Research Council: 'Assessing Public Attitudes to Health Related Findings in Research', April 2012
- World Health Organization: 'Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants', 2011
- World Health Organization: 'Guidance for Managing Ethical Issues in Infectious Disease Outbreaks', 2016
- World Health Organization: 'Research Ethics in International Epidemic Response. WHO Technical Consultation Meeting Report', 2010
- World Medical Association: 'Helsinki Declaration', 2013

7. Acronyms

ANVISA	Agência Nacional de Vigilância Sanitária (Brazilian Health Regulatory Agency)
CEPI	Coalition of Epidemic Preparedness Innovations
CIOMS	The Council for International Organizations of Medical Sciences (CIOMS)
CRO	Clinical Research Organization
EMA	European Medicines Agency
EUAL	Emergency Use Assessment and Listing Procedure
FDA	Food and Drug Administration (FDA)
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
LSLV	Last subject last visit
KFDA	Korea Food and Drug Administration
PMDA	Pharmaceuticals and Medical Devices Agency, Japan
SOP	Standard Operating Procedure
WHO	World Health Organization