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ICH guideline E6 on good clinical practice

Draft ICH E6 principles

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ICH-E6 Good Clinical Practice (GCP)

Explanatory Note

The International Council for Harmonisation (ICH) is committed to developing timely technical requirements for pharmaceuticals for human use in a manner that is responsive to the needs of the global community. ICH is committed to stakeholder engagement and transparency in the development of its guidelines.

ICH E6 Good Clinical Practice (GCP) Guideline is widely used by clinical trial researchers beyond the membership and regional representation of ICH itself and has a significant impact on trial participants and patients. Acknowledging the wide and substantial impact of ICH E6, the ICH Management Committee is making available a draft, work-in-progress version of the updated principles that are currently under development by the ICH E6(R3) Expert Working Group (EWG). The principles are interdependent and should be considered in their totality to assure ethical trial conduct, participant safety, and reliable results of clinical trials.

The renovation of ICH E6(R2) will set out principles which will be aligned with the principles in ICH E8(R1) Revision of General Considerations for Clinical Studies. ICH E8(R1) includes a framework for designing quality into clinical trials, stakeholder engagement, trial design, proportionate trial management and focus on factors critical to the quality of trials. When complete, ICH E6(R3) will be composed of an overarching principles document (the document of which a draft is now made public), Annex 1 (addressing interventional clinical trials), and Annex 2 (providing any needed additional considerations for non-traditional interventional clinical trials). The overarching principles document and Annex 1 will replace the current ICH E6(R2).

Although the EWG's work is continuing and the group is still progressing towards *Step 2* of the ICH guidance development process (<https://ich.org/page/formal-ich-procedure>), the ICH Management Committee decided that sharing the draft version of the principles would facilitate transparency and common understanding. Although public comments are not requested at this time, once the updated ICH E6 Guideline achieves *Step 2* of the ICH guidance development process, public input will be invited and considered. *Step 2* will involve simultaneous publication of both the draft principles and Annex 1, along with an introduction and a glossary. Public comment will be invited at that point since the principles need to be seen and commented on alongside the details in Annex 1.

The ICH E6(R3) EWG is organizing a web conference to present the current draft of the GCP principles as a work in progress. Additionally, the general ICH process will be presented with a focus on the ICH E6(R3) development process.

ICH E6 Principles

(Draft Version: March 2021)

Clinical trials are a fundamental part of clinical research that support the development of new medicines or uses of existing medicines. Well designed and conducted clinical trials help answer key questions in health care and drug development. Their results are essential for evidence-based healthcare decisions. Trials with inadequate design and/or poorly conducted trials may place participant safety at risk and yield inadequate or unreliable evidence. They waste resources and the efforts and time of investigators and participants.

The principles of GCP are designed to be flexible and applicable to a broad range of clinical trials. This guideline, along with ICH E8, encourages thoughtful consideration and planning to address specific and potentially unique aspects of an individual clinical trial. This includes evaluation of trial characteristics, such as the design elements, the investigational product being evaluated, the medical condition being addressed, characteristics of the participants, the setting in which the clinical trial is being conducted, and the type of data being collected. Careful consideration of factors relevant to ensuring trial quality is needed for each clinical trial.

The principles are intended to support improved and more efficient approaches to trial design and conduct. For example, innovative digital health technologies may expand the possible approaches to trial conduct. Such technologies can be incorporated in existing healthcare infrastructures and enable the use of a variety of relevant data sources in clinical trials. This will aid in keeping clinical trial conduct in line with advancing science and technological developments. The use of technology in the conduct of clinical trials should be adapted to fit the participant characteristics and the particular trial design. The use of innovative technologies may help enable those designing and conducting a trial to include relevant patient populations. This guideline is intended to be media neutral to enable the use of different technologies for the purposes of documentation.

Clinical trial designs that bring the trial to participants and their communities may improve the representativeness of the participant population and enable wider participation. The process of building quality into the design of the trial may be supported by participation of those directly involved. These may include a broad range of stakeholders, including patients and treating physicians. Their input can increase the likelihood of meaningful trial outcomes, which are relevant to both trial participants and future patients. This input will also guide decisions on the feasibility of data collection and assure that participation in the trial does not become unduly burdensome for those involved.

Clinical trials should be designed to protect the rights, safety and well-being of participants and assure the reliability of results. Clinical trial designs and processes should be proportionate to the risks inherent in the trial and the importance of the data being collected. Trial designs and processes should be evaluated to minimize unnecessary complexity and burden.

The following overarching principles provide a flexible framework for clinical trial conduct. They are structured to provide guidance throughout the lifecycle of the clinical trial. These principles are applicable to trials involving human participants, i.e., healthy volunteers or patients. The principles are interdependent and should be considered in their totality to assure ethical trial conduct and reliable results.

- 1- Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice (GCP) and applicable regulatory requirement(s).**

- 2- Clinical trials should be designed and conducted in ways that ensure the rights, safety, and well-being of participants.**
 - 2.1 The rights, safety, and well-being of the participants are the most important considerations, and should prevail over interests of science and society.
 - 2.2 The safety of the participants should be reviewed periodically, as new safety information becomes available which could have an impact on the participant or the conduct of the trial.
 - 2.3 Foreseeable risks and inconveniences should be weighed against the anticipated benefits for the individual participants and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
 - 2.4 When appropriate, the participant selection process should be representative of the anticipated population who are likely to use the medicinal product in future clinical practice. When designing a clinical trial, the scientific goal and purpose should be carefully considered so as not to unnecessarily exclude particular participant populations.
 - 2.5 A qualified physician or, when appropriate, a qualified dentist, should have the overall responsibility for the medical care given to, and medical decisions made on behalf of, participants; however, the practical interactions and the delivery of medical care and decisions can be carried out by appropriately qualified health care professionals in accordance with local regulations.
 - 2.6 The confidentiality of information that could identify participants should be protected in accordance with applicable privacy and data protection regulations.

- 3- Informed consent is an integral feature of the ethical conduct of a trial. Clinical trial participation should be voluntary and based on a consent process that ensures participants are well-informed.**
 - 3.1 Freely given informed consent should be obtained and documented from every participant prior to clinical trial participation. For participants unable to provide informed consent, their legally authorized representative should provide consent prior to clinical trial participation.
 - 3.2 The process and information provided should be designed to achieve the primary objective of enabling trial participants to make an informed decision on whether or not to participate in the trial. The informed consent process should take into consideration relevant aspects of the trial such as characteristics of the participants, the trial design, anticipated benefit and risk of medical intervention(s), setting and

context in which the trial will be conducted (e.g., trials in emergency situations), and the potential use of technology to inform participants and obtain informed consent.

4- Clinical trials should be subject to objective review by an institutional review board (IRB)/independent ethics committee (IEC).

4.1 A trial should always be conducted in compliance with the protocol that receives prior IRB/IEC approval/favourable opinion.

4.2 Periodic review of the trial by the IRB/IEC should also be conducted as appropriate.

5- Clinical trials should be scientifically sound for their intended purpose, and based on robust and current scientific knowledge and approaches.

5.1 The available nonclinical and clinical information on an investigational product(s) should be adequate to support the proposed clinical trial.

5.2 Clinical trials should be scientifically sound and reflect the state of knowledge and experience with the investigational product(s); including if applicable, the condition to be treated, diagnosed, or prevented; the current understanding of the underlying biological mechanism (of both the condition and the treatment); and the population for which the investigational product is intended.

5.3 There should be periodic review of current scientific knowledge and approaches to determine whether adjustments to the trial are needed, since new or unanticipated information may arise once the trial has begun.

6- Clinical trials should be designed and conducted by qualified individuals.

6.1 Individuals with different expertise and training are needed across all phases of a clinical trial, such as physicians, scientists, ethicists, technology experts, and statisticians. Individuals involved in a trial should be qualified by education, training, and experience to perform their respective task(s).

7- Quality should be built into the scientific and operational design and conduct of clinical trials.

7.1 Quality of a clinical trial is considered in this document as fit for purpose. The quality and amount of the information generated during a clinical trial should be sufficient to support good decision making.

7.2 Factors critical to the quality of the trial should be identified. These factors are attributes of a trial which are fundamental to the protection of participants, the reliability and interpretability of the trial results, and the decisions made based on those trial results. These quality factors are critical because, if they were to be

undermined by errors of design or conduct, the ethical basis of the trial and reliability of results could also be undermined.

7.3 Quality by design in clinical trial sets out to ensure that the quality of a trial is driven proactively by designing quality into the study protocol and processes. This may involve the use of a prospective, multidisciplinary approach to promote the quality of protocol and process design, and clear communication of how this will be achieved. Quality by design approaches should be applied across the clinical trial and supporting processes.

7.4 Strategies should be implemented to avoid, detect, and address serious non-compliance with GCP and prevent recurrence.

8- Clinical trial processes, measures, and approaches should be proportionate to the risks to participants and to the reliability of trial results.

8.1 Trial processes should be proportionate to the risks inherent in the trial and the importance of the information collected. Risks in this context include risks to the rights, safety and well-being of trial participants, as well as risks to the reliability of the trial results.

8.2 Risks beyond those of standard medical care should be the focus of considerations; however, the risks relating to investigational products which have a marketing authorisation used in the clinical trial context may differ from the usual care of patients and should be taken into consideration.

8.3 The quality factors should be prioritized at the time of the trial design to identify those that are critical to the trial.

8.4 Risks which have an impact on the quality factors considered critical to the trial should be managed.

9- Clinical trials should be described in a clear, concise, and operationally feasible protocol.

9.1 A well-designed trial protocol is a fundamental component for protection of participants and for the generation of reliable results.

9.2 The scientific objectives of any trial should be clear and explicitly stated in the protocol.

9.3 Trial processes should be operationally feasible and avoid unnecessary complexity, procedures, and data collection. Trial processes should support the study key objectives.

9.4 The clinical trial protocol as well as the plans or documents for the protocol execution (e.g., statistical analysis plan, data monitoring plan) should be clear, concise, and operationally feasible.

10- Clinical trials should generate reliable results.

- 10.1** The quality and amount of the information¹ generated in a clinical trial should be sufficient to provide confidence in the trial's results and support good decision making.
- 10.2** Systems and processes that help ensure the quality of the information generated from the clinical trial should be implemented in a way that is proportionate to the risks to participants and the reliability of trial results.
- 10.3** Tools that aid in data capture, management, and analyses should be fit for purpose, should capture the information required by the protocol, and should conform to principles that ensure reliable results.
- 10.4** Digital systems used for clinical trial purposes should consider the factors critical to their quality in their design and be fit for purpose. To this end, validation of systems, data protection, information technology (IT) security and user management are important elements that should be addressed.
- 10.5** Clinical trials should incorporate efficient and well-controlled processes for managing information through appropriate management of data integrity, traceability, and protection of personal information, thereby allowing the accurate reporting, interpretation, and verification of the clinical trial-related information.
- 10.6** Clinical trial-related information should be retained securely by sponsors and investigators for the required period of time and should be available to regulatory authorities upon request to enable reconstruction of the trial conduct and results in order to ensure reliability of trial results.
- 10.7** The transparency of clinical trials in drug development includes registration on publicly accessible and recognized databases, and the public posting of clinical trial results.
- 10.8** The principles in this section for trial information and documentation apply irrespective of the type of media used.

11- Roles, tasks and responsibilities in clinical trials should be clear and documented appropriately.

- 11.1** The sponsor and investigator may delegate some or all of their tasks but retain overall responsibility for the quality and integrity of trial conduct and the safety of participants.

¹For the purpose of this guideline, the term "information" reflects meaningful organization and processing of data and documentation and "data" reflects measurement and assessment of variable parameters relevant to specific outcomes. The "results" are a composition of organized and fit-for-purpose information.

- 11.2** Agreements should clearly define the roles, tasks and responsibilities for the clinical trial and be documented appropriately. Where tasks have been delegated or contracted to third parties, the responsibility is retained by the sponsor or investigator who should maintain appropriate oversight of these tasks.

12- Investigational products used in a clinical trial should be manufactured in accordance with applicable Good Manufacturing Practice (GMP) standards and be stored, shipped, and handled in accordance with the product specifications and the trial protocol.

- 12.1** Investigational products used in a clinical trial should be manufactured in accordance with applicable GMP.
- 12.2** Measures should be in place to ensure that the investigational product provided to trial participants retains its quality.
- 12.3** Investigational products should be used in accordance with the protocol and relevant study documents.
- 12.4** Manufacturing, handling, and labelling of investigational products should be undertaken in a manner that maintains blinding, and treatment assignment, where applicable.
- 12.5** Investigational product labelling should follow the appropriate regulatory requirements.
- 12.6** Risk-based approaches should be considered when implementing proportionate measures to ensure GMP and the appropriate shipping and handling of the investigational product.