E6(R3) Good Clinical Practice: Annex 2

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FOREWORD

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner. By harmonizing the regulatory expectations in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized safety reporting and marketing application submissions, and contributed to many other improvements in the quality of global drug development and manufacturing and the products available to patients.

ICH is a consensus-driven process that involves technical experts from regulatory authorities and industry parties in detailed technical and science-based harmonization work that results in the development of ICH guidelines. The commitment to consistent adoption of these consensus-based guidelines by regulators around the globe is critical to realizing the benefits of safe, effective, and high-quality medicines for patients as well as for industry. As a Founding Regulatory Member of ICH, the Food and Drug Administration (FDA) plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance to industry.

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GOOD CLINICAL PRACTICE (GCP)

E6(R3)

Annex 2

Draft version

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At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

E6(R3)
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ICH HARMONISED GUIDELINE

GOOD CLINICAL PRACTICE (GCP)

E6(R3) ANNEX 2

ICH Consensus Guideline

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ANNEX 2

I. INTRODUCTION

Good Clinical Practice (GCP), as described in ICH E6(R3) Principles and Annex 1, is applicable across clinical trial types, designs and settings, and remains relevant when various operational approaches and data sources are used in a clinical trial. As clinical trial designs evolve and technological advances occur, the appropriate and proportionate application of GCP will support these approaches while safeguarding participants' rights, safety and well-being, and helping to ensure the reliability of trial results. ICH E6(R3) Annex 2 addresses the GCP considerations that arise from the increased use of a wider range of design elements and data sources. Annex 2 provides additional GCP considerations, focusing on examples of trials that incorporate decentralised elements, pragmatic elements and/or real-world data (RWD). Clinical trials may incorporate one or more of the design elements and data sources mentioned above. Annex 2 is not meant to be comprehensive of all design elements since clinical trial ecosystems may continue to evolve, and the operational approaches and data sources utilised may expand. However, considerations provided in this Annex may apply in accordance with local regulatory requirements. This Annex should not be read as an endorsement of any specific trial design elements or data sources and should be read in conjunction with the Principles and Annex 1.

For the purposes of Annex 2, decentralised elements in a clinical trial are those trial-related activities conducted outside the investigator's location (e.g., trial visit is conducted in the trial participant's home, local healthcare centre or mobile medical units or when data acquisition is performed remotely using digital health technologies (DHTs)). Pragmatic elements in clinical trials are those that integrate aspects of clinical practice into the design and conduct of the trial (e.g., simplified protocols with streamlined data collection). Data may be broadly classified into two types, and a trial may make use of both types of data (i.e., data generated specifically for the trial (primary data collection) or data obtained from sources external to the trial that are collected for other purposes (secondary data use)). RWD incorporated in clinical trials include the use of data relating to patient health status collected from a variety of sources outside of clinical trials (e.g., electronic health records (EHRs), registries, claims data). These data from RWD sources

may be used in various ways, including, but not limited to, ascertaining endpoints or outcomes or serving as an external control.

Regardless of the operational approaches and data sources used, a quality by design (QbD) approach should be used in clinical trials as stated in Annex 1. The design elements, DHTs and data sources that are adopted and implemented should be fit for purpose to ensure that the quality and amount of information generated or collected are sufficient to support good decision making.

1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

The ethical principles and standards for the evaluation of clinical trials by IRBs/IECs as described in the Principles and Annex 1, provide a sound basis for the conduct of clinical trials, including those incorporating decentralised elements, pragmatic elements and/or RWD. Particular attention should be given, for example, to privacy and confidentiality of the participants and security of their data.

2. INVESTIGATOR

2.1 Communication with IRB/IEC

The investigator, in accordance with local regulatory requirements, should provide the IRB/IEC with the information needed for the evaluation of the appropriateness of various operational approaches and data sources being used (see Annex 1, section 1.1).

2.2 Informed Consent Considerations

The informed consent process is an integral part of the conduct of interventional clinical trials. Varied approaches (e.g., text, images, videos and other interactive methods) may be used in the informed consent process, including for providing information to the participant and for supporting the participant's understanding of the trial (see Annex 1, section 2.8).

The informed consent materials and process should be tailored to reflect the design elements of the trial (e.g., decentralised or pragmatic elements).

2.2.1 Informed consent may be obtained remotely, where appropriate. When informed consent is obtained remotely, the investigator should assure themselves of the identity of the

participant (or legally acceptable representative where applicable) in accordance with applicable regulatory requirements.

2.2.2 The characteristics of the trial population (e.g., participants may lack familiarity with electronic systems) and the appropriateness of the method and tools used to obtain consent should be taken into consideration when developing the informed consent materials and process. Trial participants may be given the option to use a paper-based approach and/or in-person consent process, to the extent feasible, should they prefer this.

2.2.3 The informed consent materials should describe what type of data will be collected, how the data may be used and who will have access to the trial participant's personal information, such as health records and home address (e.g., when trial-related activities are conducted at the participant's home or local healthcare centre or when data are collected remotely via DHTs).

2.3 Investigational Product Management

Various approaches to investigational product management (i.e., supply, storage, dispensing, administration, return, accountability documentation, destruction or alternative disposition) may be utilised, as appropriate. The investigational product may be dispensed or supplied to the participant or to an appropriate designee (e.g., caregiver, home nurse, local pharmacist) for administration at the participant's location (e.g., participant's home, local healthcare centre) by appropriate parties (e.g., the investigator site staff, the participant, a home nurse or a local pharmacist). These approaches should be arranged and conducted in accordance with applicable regulatory requirements. The level of investigator oversight will depend on a number of factors, including the characteristics of the investigational product, route and complexity of administration, level of existing knowledge about the investigational product's safety and marketing status (see Annex 1, section 2.10).

2.3.1 The investigator may arrange to send the investigational product to the participant (e.g., the participant's home) in accordance with applicable regulatory requirements. When shipping investigational products to a participant, the following should be considered:

(a) The process for protecting the privacy and maintaining the confidentiality of the participant and their disease status.

(b) That the investigational product is being received by the intended recipient (e.g., the participant or their appropriate designee, such as a caregiver).

(c) The process for the receipt, storage, handling, administration, return, destruction or alternative disposition and accountability of the investigational product.

(d) The process by which blinding (if applicable) is protected.

(e) The availability of participant support tools, such as online tutorials, information brochures, visual aids and contact details for support (e.g., technical support).

2.3.2 Certain documentation and processes already used in the institution/healthcare centre may be sufficient for the management of the investigational product, in accordance with local regulatory requirements. For example, existing standard pharmacy practices for product accountability and record of storage conditions that are kept routinely in the pharmacy may be appropriate.

2.3.3 The investigator should maintain appropriate oversight of the activities related to investigational product management and should ensure that appropriate documentation is maintained. See section 2.3 on the level of oversight. These activities should be under the oversight of the investigator, which include, but are not limited to:

(a) The receipt, use and return (or alternative disposition) of the investigational product by the trial participants, where appropriate. Receipt and return (or alternative disposition) may be undertaken by an appropriate designee of the participant in accordance with local regulatory requirements.

(b) Commencement, continuation, dose and dose adjustments of the allocated investigational product in accordance with the protocol.

2.4 Investigator Oversight

Healthcare professionals may be involved in performing trial-related activities that are part of clinical practice.

If knowledge about the protocol, investigator's brochure or other trial-related document is necessary to perform a trial-related activity, this activity should be performed by delegated persons or parties who are under appropriate oversight of investigator and have been appropriately trained, if needed.

For trial-related activities conducted in clinical practice by healthcare professionals which do not require knowledge about the protocol, investigators' brochure, or other trial-related documents, appropriate arrangements and appropriate investigator oversight should be in place. Such arrangements should address plans for making relevant information and records available to the investigator.

The level of investigator oversight of the trial-related activities should depend on the nature of the activities and be proportionate to the risks to trial participant safety and data reliability, and the importance of the data being collected. Such oversight should ensure that the resulting records meet the relevant requirements of the protocol and thereby ensure reliable trial results, trial-participant safety and appropriate decision-making.

2.5 Safety Assessment and Reporting

For the safety monitoring of individual trial participants (see Annex 1, section 2.7), the investigator should review and assess information on the health status of participants across the sources of safety-related information (e.g., home nursing, remote trial visits, use of DHTs). See section 3.9 and Annex 1, section 3.13.2 for details on how this information will be provided to the investigator.

3. SPONSOR

3.1 Engagement and Communication

Engagement with relevant stakeholders is particularly important when utilising various operational approaches and data sources in clinical trials. The following considerations are important in communicating with relevant stakeholders and may be undertaken in various ways taking into consideration ICH E8(R1) General Considerations for Clinical Studies.

3.1.1 Engaging patients, patient advocacy groups and their communities, as appropriate, can help ensure the successful integration and implementation of various operational approaches and data sources in trials. For example, involving patients early in the design of the trial may help ensure the suitability of DHTs (e.g., mobile apps, wearables) used in trials with decentralised elements. This engagement may bring attention to areas where additional training or support may be needed (e.g., digital literacy, physical ability or lack of access to technology that may require the use of alternative approaches, specialised training or the provision of technology).

3.1.2 Engaging healthcare professionals and/or investigators early in the design of a clinical trial that incorporates various operational approaches and data sources is critical for the successful implementation and conduct of a clinical trial. Early engagement can help:

(a) Address issues related to the infrastructure needed to conduct the trial.

(b) Develop protocols that incorporate the routine workflow of healthcare professionals, when appropriate, and that allow for the integration of RWD generated in clinical practice when such data are fit for purpose.

(c) Identify areas where training or support for healthcare professionals and/or investigators is needed.

3.1.3 Sponsors are encouraged to engage with regulatory authorities early, especially when designing and planning trials that use various operational approaches (including complex design elements and technological tools) and RWD sources. Early engagement will help address the appropriateness of using such operational approaches and RWD sources in the design of their trial and will allow for timely identification of challenges and strategies for resolution.

3.2 Protocol and Trial Design

Annex 1, Appendix B describes topics that should generally be included in the clinical trial protocol. Additional consideration may need to be given to the protocol and/or protocol-related documents when utilising various operational approaches and/or data sources so that all parties involved in the trial conduct are adequately informed.

3.2.1 The specific design elements and data sources should be adequately described in the protocol, and the appropriateness of their use justified. The rationale, fitness for purpose and feasibility of using certain design elements and data sources should be briefly explained. These descriptions can be supplemented in the protocol-related documents (see Annex 1, Appendix B).

3.2.2 Since data may originate from different sources or various practice settings (e.g., sources with different timing of data collection), there may be data variability within and/or between data sources/settings. The impact of such data variability should be considered in the trial design and discussed in the protocol or protocol-related documents (e.g., statistical analysis plan).

3.2.3 The design elements and data sources should be considered when determining the need for appropriate training and technical support to be provided to the investigator, investigator site staff and participants (see Annex 1, section 2.3.2).

3.2.4 The protocol and, where applicable, protocol-related documents should describe how safety information will be collected from the variety of data sources (e.g., by DHTs, in-person or remote visits), how emerging abnormalities potentially related to participants' safety will be identified and made available to the investigator and what actions should be taken by the investigator in these instances. Such information should be provided to the investigator in a manner that would help inform their decision making (e.g., on eligibility, treatment, continuing participation in the trial and care for the safety of the individual trial participants). See sections 2.5 and 3.9 for more information on safety assessment and reporting.

3.2.5 Modalities of the informed consent process (e.g., remote or in-person) should be described in the protocol.

3.3 Communication with IRB/IEC

The sponsor, in accordance with local regulatory requirements, should ensure that the IRB/IEC is provided with the information needed to evaluate the appropriateness of various operational approaches and data sources (see Annex 1, section 1.1).

3.4 Consent or Permission Considerations for RWD

In situations where RWD are used, the sponsor should ensure that appropriate consent or permission for the use of the data has been obtained in accordance with applicable regulatory requirements.

3.5 Data Considerations

The following section provides aspects that should be taken into consideration when utilising a variety of data sources.

3.5.1 Real-World Data Considerations.

(a) A variety of RWD sources may be used in clinical trials (e.g., EHRs, claims data, registry data). The sponsor should apply special considerations to these data sources depending on the data collection and acquisition process and if the data are primary or secondary, since the sponsor may have different levels of control over what and how data elements are collected. These considerations include, but are not limited to:

(i) The potential variability of data formats (e.g., different terminologies and/or standards) with data coming from a variety of sources.

(ii) Lack of standardised timing of data collection and procedures (e.g., the timing and frequency of clinical assessments in RWD are based on clinical practice and may have been influenced by the participant's clinical status; therefore, the protocol schedule may not match with those available from the RWD).

(iii) Missing data (e.g., due to participants moving to different healthcare systems) or the occurrence of intercurrent events between clinical visits that may be difficult to capture or ascertain when using RWD (e.g., discontinuation of treatment or the use of an additional or alternative therapy that is not captured in the EHR). See ICH E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials.

(iv) The overall quality of data collected in clinical practice (e.g., EHR, claims data) or registries, including operational processes and database structure, consistency of vocabularies and coding systems.

(v) De-identification methodologies used to protect the privacy and confidentiality of personal information of trial participants.

(vi) The validation status of tools used for the acquisition of RWD (e.g., registries), as appropriate.

(b) The sponsor should ensure the fitness for purpose of RWD, which can be described by their reliability and relevance. The term reliability includes accuracy, completeness and traceability; the term relevance includes the availability of key data elements (e.g., exposure, outcomes, covariates) to answer the specific trial question with the specific method.

(c) The RWD used in a clinical trial (e.g., data acquired during clinical practice, RWD from a third party) may be owned or controlled by entities other than the sponsor. In such cases, the sponsor should have agreements with those entities in place that allow regulatory authorities to access the source records and data for the purpose of conducting regulatory inspections in accordance with applicable regulatory requirements.

(d) Multiple data sources might need to be linked to corroborate information and to improve the completeness and reliability of RWD (e.g., linkage of data from EHRs and claims databases or linkage of a RWD source to a mortality database to confirm outcomes). When data are linked, accurate matching to the individual should be assured and the sponsor should ensure adequate measures to sufficiently protect both data privacy and reliability of trial results. If data are to be linked, this should be pre-specified in the protocol or protocol-related documents.

3.5.2 *Remote Data Collection Considerations*

(a) Remote data collection in clinical trials that incorporate decentralised and pragmatic elements (e.g., the use of remote visits and DHTs, such as wearables,

or the extraction of data from EHRs) requires special attention to be paid to data security vulnerabilities (see Annex 1, section 4.3.3), including cybersecurity and data privacy (see section 3.7).

(b) Some of the RWD considerations in section 3.5.1 may also apply to remote clinical trial data collection (e.g., DHTs including wearables).

3.6 Investigational Product Management

Various approaches to investigational product management (i.e., supply, storage, dispensing, administration, return, accountability documentation, destruction or alternative disposition) may be utilised, as appropriate (see section 2.3 and Annex 1, section 3.15.3).

3.6.1 The sponsor should assess these approaches to investigational product management during the protocol development process. This assessment should consider, for example, the stability of the investigational product and the requirement for specialised storage conditions, the necessary preparation of the final investigational product for administration (e.g., complex reconstitution or administration) and the route of administration. This assessment should also consider the trial population, the knowledge about the investigational product safety profile, the need for in-person clinical observation in the immediate post-administration period, the measures needed to protect blinding if applicable, and the need for emergency plans related to investigational product administration (e.g., requirement for rescue medication).

3.6.2 The sponsor may arrange to send the investigational product to the participant (e.g., to the participant's home) in accordance with applicable regulatory requirements. For specific considerations for investigational product shipping to the participant, see section 2.3.1.

3.6.3 The sponsor may deploy systems (e.g., interactive response technology, DHTs) and assist the investigator to establish processes (e.g., home nurse visits) to ensure that the allocated investigational product was delivered and administered appropriately to the trial participant.

3.7 Privacy and Confidentiality Considerations

Sponsors should ensure security safeguards, including cybersecurity, are in place to protect the privacy and confidentiality of personal information of trial participants. Participants' personal information may be required by service providers to fulfil their activities (e.g., disclosure of personal information when investigational product is shipped to participants or when a home nurse is deployed, where appropriate). In these circumstances sponsors and service providers should ensure that appropriate informed consent has been provided by the participant, that the personal information is protected from inadvertent disclosure and that access to these data is limited to those authorised. The sponsors should address the risk of potential disclosure of personal information from a data breach when data from DHTs and/or RWD are used.

3.8 Sponsor Oversight

Sponsor oversight of clinical trials can be more complex with the myriad of data sources, the various operational approaches to the trial design and conduct, and the number of service providers involved. Sponsors should ensure that there are processes in place to provide appropriate level of oversight such that the participants' rights, safety and well-being are protected, and the reliability of the results is ensured. Sponsor oversight includes, but is not limited to, quality control and assurance measures specifically customised to the clinical trial and its critical to quality factors and identified risks. There should be appropriate oversight of service providers including maintenance of their essential records. See Annex 1, sections 3.9, 3.10 and 3.11, and Appendix C.

3.9 Safety Assessment and Reporting

3.9.1 Safety information in clinical trials with decentralised and/or pragmatic elements may be captured in a variety of ways and may come from multiple sources. For example, some trials may capture information via remote visits, DHTs, EHRs, in-person visits or a combination thereof. In these circumstances, the sponsor should ensure that safety information is appropriately captured and made accessible to the investigator in a timely manner according to the protocol. The safety information should be provided in an actionable manner that provides the investigator with an overview on the health status of the trial participant to allow for medical decision making.

3.9.2 The approach to safety management, including any mitigating actions to safeguard participant safety, and to reporting, should be described in the protocol or protocol-related documents. This approach should take into account the trial design, the design elements and the variety of data sources. Where appropriate, consideration should be given to ICH E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials.