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ICH HARMONISED GUIDELINE

GUIDELINE FOR GOOD CLINICAL PRACTICE

E6(R3)

Final version

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ICH HARMONISED GUIDELINE

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E6(R3)

ICH Consensus Guideline

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I. INTRODUCTION

Good Clinical Practice (GCP) is an international, ethical, scientific and quality standard for the conduct of trials that involve human participants. Clinical trials conducted in accordance with this standard will help to assure that the rights, safety and well-being of trial participants are protected; that the conduct is consistent with the principles that have their origin in the Declaration of Helsinki; and that the clinical trial results are reliable. The term "trial conduct" in this document includes processes from planning to reporting, including planning, initiating, performing, recording, oversight, evaluation, analysis and reporting activities as appropriate.

The objective of this ICH GCP Guideline is to provide a unified standard to facilitate the mutual acceptance of clinical trial data for ICH member countries and regions by applicable regulatory authorities.

This guideline builds on key concepts outlined in ICH E8(R1) General Considerations for Clinical Studies. This includes fostering a quality culture and proactively designing quality into clinical trials and drug development planning, identifying factors critical to trial quality, engaging interested parties, as appropriate, and using a proportionate risk-based approach.

Clinical trials vary widely in scale, complexity and cost. Careful evaluation of critical to quality factors involved in each trial and the risks associated with these factors will help ensure efficiency by focusing on activities critical to achieving the trial objectives.

Guideline Scope

This guideline applies to interventional clinical trials of investigational products[1] that are intended to be submitted to regulatory authorities. The Principles of GCP in this guideline may also be applicable to other interventional clinical trials of investigational products that are not intended to support marketing authorisation applications in accordance with local requirements.

The Annexes provide the basis for the appropriate interpretation and application of the principles and should therefore be appropriately considered; however, various approaches to the provisions in the Annexes may be considered provided they are justified and achieve the intended purpose of the application of the principles.

This guideline encourages a risk-based and proportionate approach to the conduct of a clinical trial.

Guideline Structure

This ICH GCP Guideline is composed of Principles and Annexes that expand on the principles, with specific details for different types of clinical trials. The principles are intended to apply across clinical trial types and settings and to remain relevant as technological and

[1] For the purpose of this guideline, the term "investigational products" should be considered synonymous with drugs, medicines, medicinal products, vaccines and biological products.

methodological advances occur. The principles outlined in this guideline may be satisfied using differing approaches and should be applied to fit the intended purpose of the clinical trial.

The Annexes, including their Appendices, are intended to provide information on how the Principles can be appropriately applied to clinical trials. Additional annexes may be developed to respond to the needs of interested parties and to address emerging innovations in trial design and conduct. This guideline should be read in conjunction with other ICH guidelines relevant to the design and conduct of clinical trials, including multiregional trials.

II. PRINCIPLES OF ICH GCP

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 healthcare 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, yield inadequate or unreliable results and are unethical. 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(R1), 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, the 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 efficient approaches to trial design and conduct. For example, digital health technologies, such as wearables and sensors, may expand the possible approaches to trial conduct. Such technologies can be incorporated into 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. This guideline is intended to be media neutral to enable the use of different technologies.

The design and conduct of the clinical trial may be supported by obtaining the perspectives of interested parties, such as patients and their communities, patient advocacy groups and healthcare professionals. Their input can help to reduce unnecessary complexity, improve feasibility and increase the likelihood of meaningful trial outcomes. The use of innovative trial designs and technologies may enable the inclusion of a wider and more diverse population of participants and thereby broaden the applicability of trial outcomes.

Clinical trials should be designed to protect the rights, safety and well-being of participants and assure the reliability of results. Quality by design should be implemented to identify the factors (i.e., data and processes) that are critical to ensuring trial quality and the risks that threaten the integrity of those factors and ultimately the reliability of the trial results. Clinical trial processes and risk mitigation strategies implemented to support the conduct of the trial should be proportionate to the importance of the data being collected and the risks to trial participant

safety and the reliability of trial results. Trial designs should be operationally feasible and avoid unnecessary complexity.

The overarching principles provide a flexible framework for clinical trial conduct. They are structured to provide guidance throughout the life cycle of the clinical trial. These principles are applicable to trials involving human participants. 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 GCP and applicable regulatory requirement(s). Clinical trials should be designed and conducted in ways that ensure the rights, safety and well-being of participants.

1.1 The rights, safety and well-being of the participants are the most important considerations and should prevail over interests of science and society.

1.2 The safety of the participants should be reviewed in a timely manner as new safety information becomes available, which could have an impact on participant safety, their willingness to continue in the trial or the conduct of the trial.

1.3 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 known and anticipated risks.

1.4 When designing a clinical trial, the scientific goal and purpose should be carefully considered so as not to unnecessarily exclude particular participant populations. The participant selection process should be representative of the population groups that the investigational product is intended to benefit, once authorised, to allow for generalising the results across the broader population. Certain trials (e.g., early phase, proof of concept trials, bioequivalence studies) may not require such a heterogeneous population.

1.5 A qualified physician or, when appropriate, a qualified dentist (or other qualified healthcare professionals in accordance with local regulatory requirements) should have the overall responsibility for the trial-related 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 healthcare professionals in accordance with applicable regulatory requirements.

1.6 The confidentiality of information that could identify participants should be protected in accordance with applicable privacy and data protection requirements.

2. 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 (or their legally acceptable representatives, where applicable) are well-informed.

2.1 Freely given informed consent should be obtained and documented from every participant prior to clinical trial participation. For potential participants unable to provide informed consent, their legally acceptable representatives, acting in the participants' best interest, should provide consent prior to clinical trial participation. These potential participants should be informed about the trial in a manner that facilitates their understanding. In the event that a minor is a participant, assent should be collected from that minor, as appropriate, and in accordance with local regulatory requirements (see ICH E11(R1) Clinical Investigation of Medicinal Products in the Pediatric Population).

2.2 The process and information provided should be designed to achieve the primary objective of enabling potential trial participants to evaluate the benefits, risks and burden of participating in the trial and to make an informed decision on whether or not to participate in the trial. The information provided during the informed consent process should be clear and concise so as to be understandable by potential participants or legally acceptable representatives.

2.3 The informed consent process should take into consideration relevant aspects of the trial, such as the characteristics of the participants, the trial design, the anticipated benefits and risks of medical intervention(s), the 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 (or their legally acceptable representatives) and obtain informed consent.

2.4 In emergency situations, where consent cannot be obtained prior to trial participation, consent should be obtained from the participant or their legally acceptable representative as soon as possible in accordance with applicable regulatory requirements and the processes approved by the institutional review board/independent ethics committee (IRB/IEC).

3. Clinical trials should be subject to an independent review by an IRB/IEC.

3.1 A trial should be conducted in compliance with the protocol that received prior IRB/IEC approval/favourable opinion.

3.2 Periodic review of the trial by the IRB/IEC should also be conducted in accordance with applicable regulatory requirements.

4. Clinical trials should be scientifically sound for their intended purpose and based on adequate and current scientific knowledge and approaches.

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

4.2 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 investigational product); and the population for which the investigational product is intended.

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

5. Clinical trials should be designed and conducted by qualified individuals.

5.1 Individuals with different expertise and training may be needed across all phases of a clinical trial, such as physicians, nurses, pharmacists, scientists, ethicists, technology experts, trial coordinators, monitors, auditors and biostatisticians. Individuals involved in a trial should be qualified by education, training and experience to perform their respective task(s).

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

6.1 Quality of a clinical trial is considered in this guideline as fitness for purpose.

6.2 Factors critical to the quality of the trial should be identified prospectively. These factors are attributes of a trial that are fundamental to the protection of participants, the reliability and interpretability of the trial results and the decisions made based on those trial results. Quality by design involves focusing on critical to quality factors of the trial in order to maximise the likelihood of the trial meeting its objectives.

6.3 Strategies should be implemented to avoid, detect, address and prevent recurrence of serious noncompliance with GCP, the trial protocol and applicable regulatory requirements.

7. Clinical trial processes, measures and approaches should be implemented in a way that is proportionate to the risks to participants and to the importance of the data collected and that avoids unnecessary burden on participants and investigators.

7.1 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.

7.2 The focus should be on the risks associated with trial participation. For clinical trials involving patients, the focus should be on risks that go beyond those associated with usual medical care. The risks relating to investigational products that have a marketing authorisation when used in the clinical trial context may differ from the usual care of patients and should be taken into consideration.

7.3 Risks to critical to quality factors should be managed proactively and adjusted when new or unanticipated issues arise once the trial has begun.

7.4 Trial processes should be operationally feasible and avoid unnecessary complexity, procedures and data collection. Trial processes should support the

key trial objectives. The sponsor should not place unnecessary burden on participants and investigators.

8. Clinical trials should be described in a clear, concise, scientifically sound and operationally feasible protocol.

8.1 A well-designed trial protocol is fundamental to the protection of participants and for the generation of reliable results.

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

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

9. Clinical trials should generate reliable results.

9.1 The quality and amount of the information generated in a clinical trial should be fit for purpose and sufficient to provide confidence in the trial's results and support good decision making.

9.2 Systems and processes that aid in data capture, management and analyses, as well as those that help ensure the quality of the information generated from the trial, should be fit for purpose, should capture the data required by the protocol and should be implemented in a way that is proportionate to the risks to participants and the importance of acquired data.

9.3 Computerised systems used in clinical trials should be fit for purpose (e.g., through risk-based validation, if appropriate), and factors critical to their quality should be addressed in their design or adaptation for clinical trial purposes to ensure the integrity of relevant trial data.

9.4 Clinical trials should incorporate efficient and robust processes for managing records (including data) to help ensure that record integrity and traceability are maintained and that personal information is protected, thereby allowing the accurate reporting, interpretation and verification of the relevant clinical trial-related information.

9.5 Essential records should be retained securely by sponsors and investigators for the required period in accordance with applicable regulatory requirements. These essential records should be available to regulatory authorities, monitors, auditors and IRBs/IECs (as appropriate) upon request to enable appropriate evaluation of the trial conduct in order to ensure the reliability of trial results.

9.6 The transparency of clinical trials includes timely registration on publicly accessible and recognised databases and the public posting of clinical trial results. Communicating trial results to participants should be considered. Such communication should be objective and non-promotional.

10. Roles and responsibilities in clinical trials should be clear and documented appropriately.

10.1 The sponsor may transfer or the investigator may delegate their tasks, duties or functions (hereafter referred to as activities), but they retain overall responsibility for their respective activities.

10.2 Agreements should clearly define the roles, activities and responsibilities for the clinical trial and be documented appropriately. Where activities have been transferred or delegated to service providers, the responsibility for the conduct of the trial, including quality and integrity of the trial data, resides with the sponsor or investigator, respectively.

10.3 The sponsor or investigator should maintain appropriate oversight of the aforementioned activities.

11. Investigational products used in a clinical trial should be manufactured in accordance with applicable Good Manufacturing Practice (GMP) standards and be managed in accordance with the product specifications and the trial protocol.

11.1 Investigational products used in a clinical trial should be manufactured in accordance with applicable GMP standards.

11.2 Measures should be in place to ensure that the investigational product provided to trial participants retains its quality.

11.3 Investigational products should be used in accordance with the protocol and relevant trial documents.

11.4 Manufacturing, handling and labelling of investigational products should be undertaken in a manner that aligns with treatment assignment and maintains blinding, where applicable.

11.5 Investigational product labelling should follow applicable regulatory requirements.

11.6 Appropriate processes should be implemented for the handling, shipping, storage, dispensing, returning and destroying or alternatively disposing of the investigational product.

III. ANNEX 1

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

The IRB/IEC is responsible for the ethical review of the trial. The requirements for the IRB/IEC in this guideline should be read in conjunction with local regulatory requirements.

1.1 Submission and Communication

For the submission to or communication with the IRB/IEC, in most regions where there is also a requirement to make a submission to the relevant regulatory authority, these may be combined in a single submission in accordance with applicable regulatory requirements. Submissions and communications with the IRB/IEC and regulatory authorities are made in some regions by the investigator/institution and by the sponsor in other regions in accordance with applicable regulatory requirements.

1.2 Responsibilities

1.2.1 The purpose of an IRB/IEC is to safeguard the rights, safety and well-being of all trial participants. Appropriate consideration should be given to trials that intend to recruit vulnerable participants.

1.2.2 The IRB/IEC should review the following information, where applicable:

(a) Protocol and amendments;

(b) Informed consent material(s), assent material(s), where applicable, and any updates, including the description of the process for how informed consent and assent is to be obtained;

(c) Investigator's Brochure or current scientific information, such as a basic product information brochure (e.g., Summary of Product Characteristics (SmPC), package leaflet or labelling), as appropriate, including their updates;

(d) Other trial-related information to be provided to the trial participant(s), including a description of the media through which such information will be provided;

(e) Advertisement for participant recruitment (if used) and information on the recruitment process;

(f) Plans to compensate participants (if any);

(g) Ongoing updates to safety information;

(h) Investigator's current curriculum vitae and/or other documentation evidencing qualifications;

(i) Any other documents that the IRB/IEC may need to fulfil its responsibilities.

1.2.3 The IRB/IEC should review a proposed clinical trial within a reasonable time and document its reviews, clearly identifying the trial, the documents reviewed and the dates for the following:

(a) Approval/favourable opinion;

(b) Modifications required prior to its approval/favourable opinion;

(c) Disapproval/negative opinion;

(d) Termination/suspension of any prior approval/favourable opinion.

1.2.4 The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to participants.

1.2.5 The IRB/IEC may request more information than is outlined in section 2.8.10 be given to participants when, in the judgement of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the participants.

1.2.6 Where the protocol indicates that prior consent of the trial participant or the participant's legally acceptable representative is not possible (see section 2.8.8), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately address relevant ethical concerns and meet applicable regulatory requirements for such trials (e.g., in emergency situations).

1.2.7 If minors are to be included in a trial, the IRB/IEC should review the assent information considering the age, maturity and psychological state of the minor population intended to be enrolled, as well as applicable regulatory requirements.

1.2.8 If the trial participants are compensated for their participation in the trial, the IRB/IEC should review both the amount and method of payment to participants to assure that neither presents problems of coercion or undue influence on the trial participants. Payments to a participant should be timely, prorated and not wholly contingent on completion of the trial by the participant. Reasonable reimbursement of expenses incurred by participants, such as for travel and lodging, is not coercive.

1.2.9 The IRB/IEC should ensure that information regarding payment to participants, including the methods, amounts and schedule of payment to trial participants, is set forth in the informed consent materials and any other information to be provided to participants.

1.3 Composition, Functions and Operations

1.3.1 The IRB/IEC should consist of a reasonable number of members who collectively have the qualifications and experience to review and evaluate the science, medical aspects and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

(a) At least five members;

(b) At least one member whose primary area of interest is not in medical sciences;

(c) At least one member who is independent of the institution/investigator site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide an opinion. A list of IRB/IEC members and their qualifications should be maintained.

1.3.2 The IRB/IEC should perform its functions according to documented operating procedures, should maintain records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

1.3.3 An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its documented operating procedures, is present. Alternative processes may be applicable for expedited review (see section 1.4.5).

1.3.4 Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advice.

1.3.5 The investigator, investigator site staff and/or sponsor, where appropriate, may provide information on any aspect of the trial but should not participate in the decision making of the IRB/IEC or in the vote/opinion of the IRB/IEC.

1.3.6 An IRB/IEC may invite non-members with expertise in special areas for assistance.

1.4 Procedures

The IRB/IEC should establish, document and follow its procedures, which should include:

1.4.1 Determining its composition (names and qualifications of the members) and the authority under which it is established;

1.4.2 Scheduling, notifying its members of and conducting its meetings;

1.4.3 Conducting initial and continuing review of trials;

1.4.4 Determining the frequency of continuing review, as appropriate;

1.4.5 Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC;

1.4.6 Specifying that no participant should be enrolled in a trial before the IRB/IEC issues its documented approval/favourable opinion of the trial;

1.4.7 Specifying that no deviations from or changes to the protocol should be initiated without prior documented IRB/IEC approval/favourable opinion of an appropriate protocol amendment except when necessary to eliminate immediate hazards to the participants or, in accordance with applicable regulatory requirements, when the change(s) involves only logistical or administrative aspects of the trial;

1.4.8 Specifying that the investigator/institution should promptly report to the IRB/IEC (see section 1.1):

(a) Deviations from the protocol to eliminate immediate hazards to the trial participants (see sections 1.4.7, 2.5.4 and 2.5.5);

(b) Changes increasing the risk to participants and/or significantly affecting the conduct of the trial (see section 2.4.6);

(c) All suspected unexpected serious adverse reactions (SUSARs) in accordance with applicable regulatory requirements;

(d) New information that may adversely affect the safety of the participants or the conduct of the trial.

1.4.9 Ensuring that the IRB/IEC (see section 1.1) promptly notifies in writing (paper or electronically) the investigator/institution or sponsor concerning:

(a) Its trial-related decisions/opinions;

(b) The reasons for its decisions/opinions;

(c) Procedures for appeal of its decisions/opinions.

1.5 Records

1.5.1 The IRB/IEC should retain all relevant records (e.g., documented procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings and correspondence) in accordance with applicable regulatory requirements and make them available upon request from the regulatory authority(ies).

1.5.2 The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its documented procedures and membership lists.

2. INVESTIGATOR

2.1 Qualifications and Training

2.1.1 The investigator(s) should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial and should provide evidence of such qualifications.

2.1.2 The investigator should be familiar with the appropriate use of the investigational product(s) as described in the protocol, in the current Investigator’s Brochure, in the product information and/or in other information sources provided by the sponsor.

2.2 Resources

2.2.1 The investigator should be able to demonstrate (e.g., based on retrospective or currently available data) a potential for recruiting the proposed number of eligible participants within the recruitment period as agreed with the sponsor.

2.2.2 The investigator should have sufficient time, an adequate number of available and qualified staff, and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

2.3 Responsibilities

2.3.1 The investigator may delegate trial-related activities to other persons or parties. The investigator may be supported by the sponsor in the identification of a suitable service provider(s); however, the investigator retains the final decision on whether the service provider intended to support the investigator is appropriate based on information provided by the sponsor (see section 3.6.5).

The investigator retains the ultimate responsibility and should maintain appropriate oversight of the persons or parties undertaking the activities delegated to ensure the rights, safety and well-being of the trial participants and the reliability of data. The level of investigator oversight of the delegated activities should depend on the nature of the delegated activities and be proportionate to the importance of the data being collected and the risks to trial participant safety and data reliability.

2.3.2 The investigator should ensure that persons or parties to whom the investigator has delegated trial-related activities are appropriately qualified and are adequately informed about relevant aspects of the protocol, the investigational product(s) and their assigned trial activities (including activities conducted by staff provided by other parties in accordance with local regulatory requirements). Trial-related training to persons assisting in the trial should correspond to what is necessary to enable them to fulfil their delegated trial activities that go beyond their usual training and experience.

2.3.3 The investigator should ensure a record is maintained of the persons and parties to whom the investigator has delegated trial-related activities. Documentation of delegation should be proportionate to the significance of the trial-related activities. In situations where the activities are performed as part of clinical practice, delegation documentation may not be required.

2.3.4 Agreements made by the investigator/institution with service providers for trial-related activities should be documented.

2.3.5 The investigator/institution should permit monitoring and auditing by the sponsor, inspection by the appropriate regulatory authority(ies) and, in accordance with applicable regulatory requirements, review by IRB/IEC(s).

2.4 Communication with IRB/IEC

2.4.1 Submission to the IRB/IEC may be made by the investigator/institution or sponsor in accordance with applicable regulatory requirements (see section 1.1).

2.4.2 Before initiating a trial, the investigator/institution should have a documented and dated approval/favourable opinion from the IRB/IEC for the trial protocol, informed consent materials, participant recruitment procedures (e.g., advertisements) and any other trial-related information to be provided to participants.

2.4.3 As part of the investigator's/institution's or sponsor's (in accordance with applicable regulatory requirements) submission to the IRB/IEC, a current copy of the Investigator's Brochure or basic product information brochure should be provided (see Appendix A, section A.1.1). If the Investigator's Brochure or basic product information brochure is updated during the trial, the IRB/IEC should receive the current version in accordance with applicable regulatory requirements.

2.4.4 As the trial progresses, the investigator/institution or sponsor should provide any updates to the participant information to the IRB/IEC in accordance with applicable regulatory requirements.

2.4.5 The investigator or the sponsor should submit documented summaries of the trial status to the IRB/IEC in accordance with local regulatory requirements or upon request.

2.4.6 The investigator or the sponsor should promptly communicate to the IRB/IEC (see section 1.4.8) and, where applicable, to the institution any changes significantly affecting the conduct of the trial and/or increasing the risk to participants.

2.5 Compliance with Protocol

2.5.1 The investigator/institution should sign the protocol or an alternative contract to confirm agreement with the sponsor.

2.5.2 The investigator should comply with the protocol, GCP and applicable regulatory requirements.

2.5.3 The investigator should document all protocol deviations. In addition to those identified by the investigator themselves, protocol deviations relevant to their trial participants and their conduct of the trial may be communicated to them by the sponsor (see section 3.11.4.5.1(b)). In either case, the investigator should review the deviations, and for those deviations deemed important, the investigator should explain the deviation and implement appropriate measures to prevent a recurrence, where applicable (see section 3.9.3).

2.5.4 The investigator should follow the protocol and deviate only where necessary to eliminate an immediate hazard(s) to trial participants. In case of deviations undertaken to eliminate immediate hazard to trial participants, the investigator should inform the sponsor promptly.

2.5.5 The investigator should report information on the immediate hazard, the implemented change and the subsequent proposed protocol amendment, if any, to the IRB/IEC and, where applicable, regulatory authorities (see section 1.1).

2.6 Premature Termination or Suspension of a Trial

2.6.1 If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial participants and should ensure appropriate therapy and follow-up for the participants.

2.6.2 Where the investigator terminates or suspends their involvement in a trial without prior agreement by the sponsor, the investigator should promptly inform the institution, where applicable, the sponsor, the IRB/IEC and the regulatory authorities in accordance with applicable regulatory requirements and should provide a detailed explanation of the reasons.

2.6.3 If the sponsor terminates or suspends a trial, the investigator/institution or the sponsor, in accordance with applicable regulatory requirement(s), should promptly inform the IRB/IEC and the regulatory authorities and should provide an appropriate explanation (see section 3.17.1).

2.6.4 If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see sections 1.2.3 and 1.4.9), the investigator should inform the institution, where applicable, and the investigator/institution should promptly notify the sponsor.

2.7 Participant Medical Care and Safety Reporting

2.7.1 Medical Care of Trial Participants

(a) A qualified physician or, where appropriate, a qualified dentist (or other qualified healthcare professionals in accordance with local regulatory requirements) who is an investigator or a sub-investigator for the trial should have the responsibility for trial-related medical care and decisions.

(b) Other appropriately qualified healthcare professionals may be involved in the medical care of trial participants, in line with their normal activities and in accordance with local regulatory requirements.

(c) During and following participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a participant when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

(d) The investigator should inform the participant's primary physician about the participant's involvement in the trial if the participant has a primary physician and agrees to the primary physician being informed.

2.7.2 Safety Reporting

(a) Adverse events and/or abnormal test results required for safety evaluations (as outlined in the protocol) should be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol.

Unfavourable medical events occurring in participants before investigational product administration (e.g., during screening) should be considered and reported to the sponsor if required by the protocol.

(b) All serious adverse events (SAEs) should be reported immediately (after the investigator reasonably becomes aware of the event) to the sponsor. The investigator should also include an assessment of causality. In accordance with applicable regulatory requirements, the protocol may identify SAEs not requiring immediate reporting; for example, deaths or other events that are endpoints. Subsequent information should be submitted as a follow-up report, as necessary.

(c) For reported deaths, the investigator should supply the sponsor, the IRB/IEC and, where applicable, the regulatory authority with any additional requested information (e.g., autopsy reports and terminal medical reports) when they become available.

(d) The investigator may delegate activities for safety reporting to qualified investigator site staff but retains the overall responsibility for safety of participants under their responsibility and compliance with the reporting requirements.

2.8 Informed Consent of Trial Participants

2.8.1 In obtaining and documenting informed consent (paper or electronic format), the investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The informed consent process should include the following:

(a) Prior to consenting and enrolling participants, the investigator should have the IRB/IEC's documented approval/favourable opinion of the informed consent materials and process;

(b) The information should be as clear and concise as possible, use simple language and avoid unnecessary volume and complexity. This is to ensure that the trial participants or their legally acceptable representatives have an adequate understanding of the objectives of the trial, alternative treatments, potential benefits and risks, burdens, their rights and what is expected of the participants to be able to make an informed decision as to their participation in the trial;

(c) 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. The characteristics of the potential trial population (e.g., participants may lack familiarity with computerised systems) and the suitability of the method of obtaining consent should be taken into consideration when developing the informed consent materials and process. When computerised systems are used to obtain informed consent, trial

participants may be given the option to use a paper-based approach as an alternative.

(d) Obtaining consent remotely may be considered where appropriate.

(e) Whether the informed consent process takes place in person or remotely, the investigator should assure themselves of the identity of the participant (or legally acceptable representative) in accordance with applicable regulatory requirements.

2.8.2 The participant or the participant's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue trial participation. The communication of this information and confirmation of the willingness to continue trial participation should be documented.

New information that could impact a participant's willingness to continue participation should be assessed to determine if re-consent is needed (e.g., depending on the stage of the trial, consideration should be given to whether the new information is relevant only to new participants or to existing participants). If re-consent is needed (e.g., information on emerging safety concerns), new information should be clearly identified in the revised informed consent materials. Revised informed consent materials should receive the IRB/IEC's approval/favourable opinion in advance of use.

2.8.3 Neither the investigator nor the investigator site staff should coerce or unduly influence a participant to participate or to continue their participation in the trial.

2.8.4 None of the information provided to the participant or the participant's legally acceptable representative during the informed consent process should contain any language that causes the participant to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor or their service providers from liability for negligence.

2.8.5 The informed consent process should be conducted by the investigator or other investigator site staff delegated by the investigator, in accordance with applicable regulatory requirements. If the participant is unable to provide consent themselves (e.g., minors, patients with severely impaired decision making capacity), the participant's legally acceptable representative should provide their consent on behalf of the participant.

2.8.6 Before informed consent may be obtained, the investigator or investigator site staff delegated by the investigator, in accordance with the protocol and conditions of IRB/IEC favourable opinions/approvals, should provide the participant or the participant's legally acceptable representative ample time unless justified (e.g., in an emergency situation) and opportunity to enquire about trial details and to decide whether or not to participate in the trial. Questions about the trial should be answered to the satisfaction of the participant or the participant's legally acceptable representative.

2.8.7 Prior to trial participation, the informed consent form should be signed and dated by the participant or by the participant's legally acceptable representative and, where appropriate, by an impartial witness and by the investigator or delegated investigator site staff who conducted the informed consent discussion. By signing the consent form, the investigator or delegated investigator site staff attests that the informed consent was freely given by the participant or the participant's legally acceptable representative and the consent information was accurately explained to and apparently understood by the participant or the participant's legally acceptable representative. The informed consent process may involve a physical or an electronic signature and date (see the glossary term "signature").

2.8.8 In emergency situations, when prior consent of the participant is not possible, the consent of the participant's legally acceptable representative, if present, should be requested. When prior consent of the participant is not possible and the participant's legally acceptable representative is not available, enrolment of the participant should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the participant's rights, safety and well-being and to ensure compliance with applicable regulatory requirements. The participant or the participant's legally acceptable representative should be informed about the trial as soon as possible, and consent as appropriate should be requested.

2.8.9 If a participant or the legally acceptable representative is unable to read, an impartial witness should be present (remotely or in-person) during the entire informed consent discussion. After the informed consent form and any other information is read and explained to the participant or the participant's legally acceptable representative and they have orally consented to the participant's trial participation and, if capable of doing so, have signed and dated the informed consent form, the witness should sign and date the consent form. By signing the consent form, the witness attests that the consent information was accurately explained to and apparently understood by the participant or the participant's legally acceptable representative and that informed consent was freely given by the participant or the participant's legally acceptable representative.

2.8.10 The informed consent discussion and the informed consent materials to be provided to participants should explain the following as applicable:

(a) The purpose of the trial;

(b) That the trial involves research and summary of the experimental aspects of the trial;

(c) The trial's investigational product(s) and the probability for random assignment to the investigational product, if applicable;

(d) The trial procedures to be followed including all invasive procedures;

(e) What is expected of the participants;

(f) The reasonably foreseeable risks or inconveniences to the participant and, when applicable, the participant's partner, to an embryo, foetus or nursing infant;

(g) The reasonably expected benefits. When there is no intended clinical benefit to the participant, the participant should be made aware of this;

(h) The alternative procedure(s) or course(s) of treatment that may be available to the participant and their important potential benefits and risks;

(i) The compensation and/or treatment available to the participant in the event of trial-related injury;

(j) Any anticipated prorated compensation to the participant for trial participation;

(k) Any anticipated expenses to the participant for trial participation;

(l) That the participant's trial participation is voluntary, and the participant may decide to stop taking the investigational product or withdraw from the trial at any time, without penalty or loss of benefits to which the participant is otherwise entitled;

(m) The follow-up procedure for participants who stopped taking the investigational product, withdrew from the trial or were discontinued from the trial;

(n) The process by which the participant's data will be handled, including in the event of the withdrawal or discontinuation of participation in accordance with applicable regulatory requirements;

(o) That by agreeing to participate in the trial, the participant or their legally acceptable representative allows direct access to source records, based on the understanding that the confidentiality of the participant's medical record will be safeguarded. This access is limited for the purpose of reviewing trial activities and/or reviewing or verifying data and records by the regulatory authority(ies) and the sponsor's representatives, for example, monitor(s) or auditor(s), and in accordance with applicable regulatory requirements, the IRB/IEC(s);

(p) That records identifying the participant will be kept confidential and, to the extent permitted by the applicable regulatory requirements, will not be made publicly available. If the trial results are published, the participant's identity will remain confidential. The trial may be registered on publicly accessible and recognised databases, per applicable regulatory requirements;

(q) That the participant or the participant's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue trial participation;

(r) The person(s) to contact for further trial information and the trial participant's rights, and whom to contact in the event of suspected trial-related injury;

(s) The foreseeable circumstances and/or reasons under which the participant's trial participation may be terminated;

(t) The expected duration of the participant's trial participation;

(u) The approximate number of participants involved in the trial;

(v) That trial results and information on the participant's actual treatment, if appropriate, will be made available to them should they desire it when this information is available from the sponsor.

2.8.11 Prior to participation, the participant or the participant's legally acceptable representative should receive a copy (paper or electronic) of the signed and dated informed consent form and any other informed consent materials provided, in accordance with applicable regulatory requirements. During trial participation, the participant or the participant's legally acceptable representative should receive a copy of the consent form updates and any other updated informed consent materials provided.

2.8.12 Where a minor is to be included as a participant, age-appropriate assent information should be provided and discussed with the minor as part of the consent process, and assent from the minor to enrol in the trial should be obtained as appropriate. A process for consent should be considered if, during the course of the trial, the minor reaches the age of legal consent, in accordance with applicable regulatory requirements.

2.8.13 When a clinical trial includes participants who may only be enrolled in the trial with the consent of the participant's legally acceptable representative, the participants should be informed about the trial in a manner that facilitates their understanding and, if capable, the participant should sign and date the informed consent form or assent form as appropriate.

2.9 End of Participation in a Clinical Trial

2.9.1 When a participant decides to stop treatment with the investigational product or withdraw from a trial; is discontinued from the trial; or reaches the routine end of the trial, the investigator should follow the protocol and/or other protocol-related documents. For participants who did not reach the routine end of the trial, this may include instructions to avoid loss of already collected data, in accordance with applicable regulatory requirements, to ensure that trial results are reliable. In general, loss of already collected data may bias results and may lead to, for example, inaccurate conclusions regarding the safety profile of the investigational product.

2.9.2 Although a participant is not obliged to provide a reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights. The investigator should consider if a discussion with the participant or the participant's legally acceptable representative is appropriate. This discussion should focus on the reasons for

withdrawal to determine if there are ways to address the concerns such that the participant could reconsider their withdrawal without unduly influencing the participant's decision. The investigator or delegated investigator site staff should consider explaining to the participant the value of continuing their participation to minimise trial participants withdrawal. In this process, the investigator should ensure that it does not interfere with the participant's decision to refuse or withdraw participation at any time.

2.9.3 Where relevant, the investigator should inform the participant about the trial results and treatment received when this information is available from the sponsor after unblinding, with due respect to the participant's preference to be informed.

2.10 Investigational Product Management

2.10.1 Responsibility for investigational product(s) management, including accountability, handling, dispensing, administration and return, rests with the investigator/institution. The sponsor may facilitate aspects of investigational product management (e.g., by providing forms and technical solutions, such as computerised systems, and arranging distribution of investigational product to trial participants).

2.10.2 When the investigator/institution delegates some or all of their activities for investigational product(s) management to a pharmacist or another individual in accordance with local regulatory requirements, the delegated individual should be under the oversight of the investigator/institution.

2.10.3 Where the investigator has delegated activities related to investigational product management or aspects of these activities have been facilitated by the sponsor, 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.

2.10.4 The investigator/institution and/or a pharmacist or other appropriate individual should maintain records of the product's delivery, the inventory, the use by each participant (including documenting that the participants were provided the doses specified by the protocol) and the return to the sponsor and destruction or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable) and the unique code numbers assigned to the investigational product(s) and trial participants. For authorised medicinal products, alternative approaches to the aforementioned may be considered, in accordance with local regulatory requirements.

2.10.5 The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).

2.10.6 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

2.10.7 Where applicable, the investigator or a person designated by the investigator/institution should explain the correct use of the investigational product(s)

to each participant and should check, at intervals appropriate for the trial, that each participant is following the instructions properly.

2.10.8 The investigational product may be shipped to the participant's location or supplied to/dispensed at a location closer to the participant (e.g., at a local pharmacy or a local healthcare centre). The investigational product may be administered at the participant's location by investigator site staff, the participant themselves, a caregiver or a healthcare professional.

2.10.9 Investigational product management should be arranged and conducted in accordance with applicable regulatory requirements, and safeguards should be in place to ensure product integrity, product use per protocol and participant safety.

2.11 Randomisation Procedures and Unblinding

The investigator should follow the trial's randomisation procedures, if any, and, in the case of an investigator-blinded trial, should ensure that the treatment randomisation code is broken only in accordance with the protocol. In the case of an emergency, to protect participant safety, the investigator should be prepared and capable from the start of the trial to perform unblinding without undue delay and hindrance. The investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, emergency unblinding to protect trial participant, unblinding due to an SAE) of the investigational product(s).

2.12 Records

2.12.1 In generating, recording and reporting trial data, the investigator should ensure the integrity of data under their responsibility, irrespective of the media used.

2.12.2 The investigator/institution should maintain adequate source records that include pertinent observations on each of the trial participants under their responsibility. Source records should be attributable, legible, contemporaneous, original, accurate and complete. Changes to source records should be traceable, should not obscure the original entry and should be explained if necessary (via an audit trail). The investigator should define what is considered to be a source record(s), the methods of data capture and their location prior to starting the trial and should update this definition when needed. Unnecessary transcription steps between the source record and the data acquisition tool should be avoided.

2.12.3 The investigator should be provided with timely access to data by the sponsor (see section 3.16.1(k)) and be responsible for the timely review of data, including relevant data from external sources that can have an impact on, for example, participant eligibility, treatment or safety (e.g., central laboratory data, centrally read imaging data, other institution's records and, if appropriate, electronic patient-reported outcome (ePRO) data). The protocol may provide exceptions for access, for instance, to protect blinding.

2.12.4 The investigator should ensure that data acquisition tools and other systems deployed by the sponsor are used as specified in the protocol or trial-related instructions.

2.12.5 The investigator should ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the data acquisition tools completed by the investigator site (e.g., case report form (CRF)) and in any other required reports (e.g., SAE reports). The investigator should review and endorse the reported data at important milestones agreed upon with the sponsor (e.g., interim analysis) (see section 3.16.1(o)).

2.12.6 Data reported to the sponsor should be consistent with the source records or the discrepancies explained. Changes or corrections in the reported data should be traceable, should be explained (if necessary) and should not obscure the original entry.

2.12.7 The investigator/institution should implement appropriate measures to protect the privacy and confidentiality of personal information of trial participants in accordance with applicable regulatory requirements on personal data protection.

2.12.8 Data reported to the sponsor should be identified by an unambiguous participant code that can be traced back to the identity of the participant by the investigator/institution.

2.12.9 For systems deployed by the investigator/institution that maintain and retain trial data/information, the investigator/institution should ensure that such data are protected from unauthorised access, disclosure, dissemination or alteration and from inappropriate destruction or accidental loss.

2.12.10 When using computerised systems in a clinical trial, the investigator/institution should do the following:

(a) For systems deployed by the investigator/institution, ensure that appropriate individuals have secure and attributable access;

(b) For systems deployed by the sponsor, notify the sponsor when access permissions need to be changed or revoked from an individual;

(c) For systems deployed by the investigator/institution specifically for the purposes of clinical trials, ensure that the requirements for computerised systems in section 4 are addressed proportionate to the risks to participants and to the importance of the data;

(d) Where equipment for data acquisition is provided to trial participants by the investigator, ensure that traceability is maintained and that participants are provided with appropriate training;

(e) Ensure that incidents in the use and operation of computerised systems, which in the investigator's/institution's judgement may have a significant and/or persistent impact on the trial data or system security, are reported to the sponsor and, where applicable, to the IRB/IEC.

2.12.11 The investigator/institution should maintain the trial records as specified in Appendix C and as required by the applicable regulatory requirement(s). The investigator/institution should have control of all essential records generated by the investigator/institution before and during the conduct of the trial.

2.12.12 The investigator/institution should retain the essential records for the required retention period in accordance with applicable regulatory requirements or until the sponsor informs the investigator/institution that these records are no longer needed, whichever is the longest. The investigator/institution should take measures to ensure availability, accessibility and readability and to prevent unauthorised access and accidental or premature destruction of these records (see Appendix C).

2.12.13 The investigator/institution should keep the sponsor informed of the name of the person responsible for maintaining the essential records during the retention period; for example, when the investigator site closes or an investigator leaves the site.

2.12.14 Upon request of the monitor, auditor, IRB/IEC or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

2.13 Reports

Upon completion of the trial, the investigator, where applicable, should inform the institution. The investigator/institution should provide the IRB/IEC with a summary of the trial's outcome and, if applicable, the regulatory authority(ies) with any required reports.

3. SPONSOR

The responsibility of the sponsor entails the implementation of risk-proportionate approaches to ensure the rights, safety and well-being of the trial participants and the reliability of the trial results throughout the clinical trial life cycle.

3.1 Trial Design

3.1.1 When planning trials, the sponsor should ensure that sufficient safety and efficacy data (e.g., from nonclinical studies and/or clinical trials and/or real-world sources) are available to support human exposure by the route, at the dosages, for the duration and in the trial population to be studied.

3.1.2 Sponsors should incorporate quality into the design of the clinical trial by identifying factors that are critical to the quality of the trial and by managing risks to those factors.

3.1.3 Sponsors should consider inputs from a wide variety of interested parties, for example, healthcare professionals and patients, to support the development plan and clinical trial protocols as described in ICH E8(R1) and when developing the informed consent materials and any other participant-facing information.

3.1.4 The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures and data collection. Protocols, data acquisition tools and other operational documents should be fit for purpose, clear, concise and consistent. The sponsor should not place unnecessary burden on participants and investigators.

3.2 Resources

The sponsor should ensure that sufficient resources are available to appropriately conduct the trial.

3.3 Allocation of Activities

Prior to initiating clinical trial activities, the sponsor should determine the roles and allocate their trial-related activities accordingly.

3.4 Qualification and Training

The sponsor should utilise appropriately qualified individuals for the activities to which they are assigned (e.g., biostatisticians, clinical pharmacologists, physicians, data scientists/data managers, auditors and monitors) throughout the trial process.

3.4.1 Medical Expertise

The sponsor should have medical personnel readily available who will be able to advise on specific trial-related medical questions or problems.

3.5 Financing

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

3.6 Agreements

3.6.1 Agreements made by the sponsor with the investigator/institution, service providers and any other parties (e.g., independent data monitoring committee (IDMC), adjudication committee) involved with the clinical trial should be documented prior to initiating the activities.

3.6.2 Agreements should be updated when necessary to reflect significant changes in the activities transferred.

3.6.3 The sponsor should obtain the investigator's/institution's and, where applicable, service provider's agreements:

(a) To conduct the trial in accordance with the approved protocol and in compliance with GCP and applicable regulatory requirement(s);

(b) To comply with procedures for data recording/reporting;

(c) To retain the essential records for the required retention period in accordance with applicable regulatory requirements or until the sponsor informs the investigator/institution or, where applicable, the service provider that these records are no longer needed, whichever is longest;

(d) To permit monitoring and auditing by sponsors, inspections by regulatory authorities (domestic and foreign) and, in accordance with applicable regulatory requirements, review by IRBs/IECs, including providing direct access to source records and facilities, including to those of service providers.

3.6.4 Any of the sponsor's trial-related activities that are transferred to and assumed by a service provider should be documented in an agreement. The sponsor's trial-related activities that are not specifically transferred to and assumed by a service provider are retained by the sponsor.

3.6.5 The sponsor should provide information to the investigator on any service provider identified by the sponsor to undertake any activities under the responsibility of the investigator. The responsibility for such activities remains with the investigator (see section 2.3.1).

3.6.6 A sponsor may transfer any or all of the sponsor's trial-related activities to a service provider in accordance with applicable regulatory requirements; however, the ultimate responsibility for the sponsor's trial-related activities, including protection of participants' rights, safety and well-being and reliability of the trial data, resides with the sponsor. Any service provider used to perform clinical trial activities should implement appropriate quality management and report to the sponsor incidents that might have an impact on the safety of trial participants and/or trial results.

3.6.7 The sponsor is responsible for assessing the suitability of and selecting the service provider to ensure that they can adequately undertake the activities transferred to them. The sponsor should provide the service providers with the protocol where necessary as well as any other documents required for them to perform their activities.

3.6.8 The sponsor should have access to relevant information (e.g., SOPs and performance metrics) for selection and oversight of service providers.

3.6.9 The sponsor should ensure appropriate oversight of important trial-related activities that are transferred to service providers, including activities further subcontracted by the service provider.

3.6.10 Trial-related activities performed by service providers should be conducted in accordance with relevant GCP requirements, which may be fulfilled by a service provider's existing quality management processes that were not designed specifically to be GCP-compliant but are fit for purpose in the context of the trial.

3.6.11 A clinical trial may have one or several sponsors where permitted in accordance with applicable regulatory requirements. In trials with more than one sponsor, the sponsors should have a documented agreement that sets out their respective responsibilities, in accordance with local regulatory requirements and/or practice. Where the documented agreement does not specify to which sponsor a given responsibility is attributed, that responsibility lies with all sponsors.

3.7 Investigator Selection

3.7.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by education, training and experience and should demonstrate they have adequate resources and facilities to properly conduct the trial. If a coordinating committee and/or coordinating investigator(s) are to be utilised in multicentre trials, their organisation and/or selection are the sponsor's responsibility, and their roles and responsibilities should be documented prior to their involvement in the trial.

3.7.2 The sponsor should provide the potential investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure as well as sufficient time for the review of the protocol and the information provided.

3.8 Communication with IRB/IEC and Regulatory Authority(ies)

3.8.1 Notification/Submission to Regulatory Authority(ies)

In accordance with applicable regulatory requirement(s), before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator) should submit any required application(s) to the appropriate regulatory authority(ies) for review, acceptance and/or permission to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

3.8.2 Confirmation of Review by IRB/IEC

(a) Where reference is made to a submission to the IRB/IEC, this can be made by the investigator/institution or sponsor in accordance with applicable regulatory requirements (see section 1.1).

(b) The sponsor should ensure that the following is obtained:

(i) The name and address of the relevant IRB/IEC along with:

(aa) A statement that it is organised and operates according to GCP and the applicable regulatory requirements;

(bb) Documented initial and subsequent IRB/IEC approval/favourable opinion as well as any termination of the trial or the suspension of approval/favourable opinion.

3.9 Sponsor Oversight

3.9.1 The sponsor should ensure that the trial design and trial conduct, the processes undertaken and the information and data generated are of sufficient quality to ensure reliable trial results, trial participants' safety and appropriate decision making.

3.9.2 The sponsor should ensure that trial processes are conducted in compliance with the trial protocol and related documents as well as with applicable regulatory requirements and ethical standards.

3.9.3 The sponsor should determine necessary trial-specific criteria for classifying protocol deviations as important. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy and/or reliability of the trial data or that may significantly affect a participant's rights, safety or well-being.

3.9.4 Decisions related to the trial should be appropriately assessed for their impact on participant's rights, safety and well-being and the reliability of trial results. Risks related to such decisions should be suitably managed throughout the planning, conduct and reporting of the trial.

3.9.5 The range and extent of oversight measures should be fit for purpose and tailored to the complexity of and risks associated with the trial. The selection and oversight of investigators and service providers are fundamental features of the oversight process. Oversight by the sponsor includes quality assurance and quality control processes relating to the trial-related activities of investigators and service providers.

3.9.6 The sponsor should ensure appropriate and timely escalation and follow-up of issues to allow the implementation of appropriate actions in a timely manner.

3.9.7 The sponsor may consider establishing an IDMC to assess the progress of a clinical trial, including the safety data and the efficacy endpoints, at intervals and to recommend to the sponsor whether to continue, modify or stop a trial.

3.9.8 Where appropriate, sponsors may also establish an endpoint assessment/adjudication committee in certain trials to review endpoints reported by investigators to determine whether the endpoints meet protocol-specified criteria. To minimise bias, such committees should typically be blinded to the assigned treatments when performing their assessments, regardless of whether the trial itself is conducted in a blinded manner.

3.9.9 Committees established for purposes that could impact participant safety or the reliability of trial results should include members with relevant expertise and with managed conflicts of interest, have written operating procedures (e.g., charters) and document their decisions.

3.10 Quality Management

The sponsor should implement an appropriate system to manage quality throughout all stages of the trial process. Quality management includes the design and implementation of efficient clinical trial protocols, including tools and procedures for trial conduct (including for data collection and management), in order to ensure the protection of participants' rights, safety and well-being and the reliability of trial results. The sponsor should adopt a proportionate and risk-based approach to quality management, which involves incorporating quality into the design of the clinical trial (i.e., quality by design) and identifying those factors that are likely to have a meaningful impact on participants' rights, safety and well-being and the reliability of the results (i.e., critical to quality factors as described in ICH E8(R1)). The sponsor should describe the quality management approach implemented in the trial in the clinical trial report (see ICH E3 Structure and Content of Clinical Study Reports).

3.10.1 Risk Management

A proportionate approach to the identification and management of risk is described below:

3.10.1.1 Risk Identification

The sponsor should identify risks that may have a meaningful impact on critical to quality factors prior to trial initiation and throughout trial conduct. Risks should be considered across the processes and systems, including computerised systems, used in the clinical trial (e.g., trial design, participant selection, informed consent process, randomisation, blinding, investigational product administration, data handling and service provider activities).

3.10.1.2 Risk Evaluation

The sponsor should evaluate identified risks and existing controls in place to mitigate the risk by considering:

(a) The likelihood of harm/hazard occurring;

(b) The extent to which such harm/hazard would be detectable;

(c) The impact of such harm/hazard on trial participant protection and the reliability of trial results.

3.10.1.3 Risk Control

Risk control should be proportionate to the importance of the risk to participants' rights, safety and well-being and the reliability of trial results. Risk mitigation activities may be incorporated, for example, in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, and training.

Where relevant, the sponsor should set pre-specified acceptable ranges (e.g., quality tolerance limits at the trial level) to support the control of risks to critical to quality factors. These pre-specified ranges reflect limits that when exceeded have the potential to impact participant safety or the reliability of trial results. Where deviation beyond these ranges is detected, an evaluation should be performed to determine if there is a possible systemic issue and if action is needed.

3.10.1.4 Risk Communication

The sponsor should document and communicate the identified risks and mitigating activities, if applicable, to those who are involved in taking action or are affected by such activities. Communication also facilitates risk review and continual improvement during clinical trial conduct.

3.10.1.5 Risk Review

The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience. Additional risk control measures may be implemented as needed.

3.10.1.6 Risk Reporting

The sponsor should summarise and report important quality issues (including instances in which acceptable ranges are exceeded, as detailed in section 3.10.1.3) and the remedial actions taken and document them in the clinical trial report (see ICH E3).

3.11 Quality Assurance and Quality Control

The sponsor is responsible for establishing, implementing and maintaining appropriate quality assurance and quality control processes and documented procedures to ensure that trials are conducted and data are generated, recorded and reported in compliance with the protocol, GCP and the applicable regulatory requirement(s).

3.11.1 Quality Assurance

Quality assurance should be applied throughout the clinical trial and includes implementing risk-based strategies to identify potential or actual causes of serious noncompliance with the protocol, GCP and/or applicable regulatory requirements to enable their corrective and preventive actions.

3.11.2 Audit

When performed, audits should be conducted in a manner that is proportionate to the risks associated with the conduct of the trial (see section 3.10.1.1).

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate whether the processes put in place to manage and conduct the trial are appropriate to ensure compliance with the protocol, GCP and the applicable regulatory requirements.

3.11.2.1 Selection and Qualification of Auditors

(a) The sponsor should appoint individuals who are independent of the clinical trial/processes being audited.

(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly.

3.11.2.2 Auditing Procedures

(a) The sponsor should ensure that the auditing of clinical trials/processes is conducted in accordance with the sponsor's documented procedures on what

to audit, how to audit (i.e., on-site and/or remote), the frequency of audits and the form and content of audit reports.

(b) The sponsor's audit plan, program and procedures for a trial audit should be guided, for example, by the importance of the trial to submissions to regulatory authorities, the number of participants in the trial, the type and complexity of the trial, the level of risks to the trial participants and any identified problem(s).

(c) The observations and findings of the auditor(s) should be documented.

(d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case-by-case basis (i.e., when evidence or suspicion of serious GCP noncompliance exists or in the course of legal proceedings).

(e) When required by applicable regulatory requirements, the sponsor should provide an audit certificate.

3.11.3 Quality Control

Quality control should be applied using a risk-based approach to each stage of the data handling to ensure that data are reliable and have been processed correctly. Within clinical trials, monitoring and data management processes are the main quality control activities. Where appropriate, quality control activities may also be applied to facilities outside of investigator sites (e.g., central image reading facilities).

3.11.4 Monitoring

The aim of monitoring is to ensure the participants' rights, safety and well-being and the reliability of trial results as the trial progresses. Monitoring is one of the principal quality control activities.

Monitoring involves a broad range of activities including, but not limited to, communication with investigator sites, verification of the investigator and investigator site staff qualifications and site resources, training and review of trial documents and information using a range of approaches including source data review, source data verification, data analytics and visits to institutional facilities undertaking trial-related activities. Some of these monitoring activities (e.g., centralised monitoring) may be conducted by different methods and persons with different roles (e.g., data scientist). However, monitoring should be performed by persons not involved in the clinical conduct of the trial at the site being monitored. The monitoring approach should consider the activities and services involved, including decentralised settings, and be included in the monitoring plan. Monitors and other trial staff should adhere to data protection and confidentiality requirements in accordance with applicable regulatory requirements, institution policy and established data security standards.

Monitoring may include site monitoring (performed on-site and/or remotely) and centralised monitoring, depending on the monitoring strategy and the design of the clinical trial.

The sponsor should determine the appropriate extent and nature of monitoring based on identified risks. Factors such as the objective, purpose, design, complexity, blinding, number of trial participants, investigational product, current knowledge of the safety profile and endpoints of the trial should be considered.

3.11.4.1 Investigator Site Monitoring

(a) Monitoring may be performed in relation to the clinical trial activities at the investigator sites (including their pharmacies and local laboratories, as appropriate). The frequency of monitoring activities should also be determined based on identified risks. Monitoring activities and their frequency should be modified as appropriate using knowledge gained.

(b) This monitoring activity may be performed on-site and/or remotely depending on the nature of the activity and its objectives.

(c) Monitoring may include remote and secure, direct read-only access to source records, other data acquisition tools and essential record retention systems.

3.11.4.2 Centralised Monitoring

(a) Centralised monitoring is an evaluation of accumulated data, performed in a timely manner, by the sponsor's qualified and trained persons (e.g., medical monitor, data scientist/data manager, biostatistician).

(b) Centralised monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of site monitoring or be used on its own. Use of centralised data analytics can help identify systemic or site-specific issues, including protocol noncompliance and potentially unreliable data.

(c) Centralised monitoring may support the selection of sites and/or processes for targeted site monitoring.

3.11.4.3 Monitoring Plan

The sponsor should develop a monitoring plan that is tailored to the identified potential safety risks, the risks to data quality and/or other risks to the reliability of the trial results. Particular attention should be given to procedures relevant to participant safety and to trial endpoints. The plan should describe the monitoring strategy, the monitoring activities of all the parties involved, the various monitoring methods and tools to be used, and the rationale for their use. The monitoring strategy should ensure appropriate oversight of trial conduct and consider site capabilities and the potential burden. The plan should focus on aspects that are critical to quality. The monitoring plan should reference the sponsor's applicable policies and procedures.

Monitoring of important data and processes (e.g., those related to primary endpoints and key secondary endpoints and processes intended to ensure participant safety) performed outside the investigator site (e.g., central image reading facilities, central laboratories) should be addressed in the monitoring plan.

3.11.4.4 Monitoring Procedures

Persons performing monitoring should follow the sponsor's monitoring plan and applicable monitoring procedures.

3.11.4.5 Monitoring Activities

Monitoring in accordance with the sponsor's requirements and monitoring plan should generally include the following activities across the clinical trial life cycle, as applicable.

3.11.4.5.1 Communication with Parties Conducting the Trial

(a) Establishing and maintaining a line of communication between the sponsor and the investigator and other parties and individuals involved in the trial conduct (e.g., centrally performed activities). In general, each site should have an assigned monitor as their contact point.

(b) Informing the investigator or other parties and individuals involved in the trial conduct of relevant deviations from the protocol, GCP and the applicable regulatory requirements and, if necessary, taking appropriate action designed to prevent recurrence of the detected deviations. Important deviations should be highlighted and should be the focus of remediation efforts as appropriate.

(c) Informing the investigator or other parties and individuals involved in the trial conduct of entry errors or omissions in source record(s) and/or data acquisition tools and ensuring that corrections, additions or deletions are made as appropriate, dated and explained (if necessary) and that approval of the change is properly documented.

(d) Actions taken in relation to the deviations, errors or omissions should be proportionate to their importance.

3.11.4.5.2 Investigator Site Selection, Initiation, Management and Close-out

(a) Selecting the site and confirming that the investigator and individuals or parties involved in the trial conduct have adequate qualifications, resources (see sections 2.1, 2.2 and 3.7) and facilities, including laboratories, equipment and investigator site staff, to conduct the trial safely and properly.

(b) Confirming, with consideration of their delegated activities and experience, that the investigator, investigator site staff, and other parties and individuals involved in the trial conduct are adequately informed

about the trial and follow the current approved protocol and other protocol-related documents, such as the current Investigator's Brochure and relevant information related to the investigational product.

(c) Confirming that the investigator is maintaining the essential records (see Appendix C).

(d) Confirming that informed consent was obtained before participation in the trial (see section 2.8) for trial participants at the site.

(e) Determining whether adverse events are appropriately reported within the time periods required by the protocol, GCP and the applicable regulatory requirement(s).

(f) Confirming the protocol requirements for source records and the site's location of such data.

(g) Verifying that the blinding is maintained, where applicable.

(h) Reviewing and reporting the participant recruitment and retention rates.

(i) Confirming that the investigator provides the required reports, notifications or other information in accordance with the protocol and trial procedures.

(j) Confirming the arrangement for the retention of the essential records and the final accountability of the investigational product (e.g., return and destruction or alternative disposition, if appropriate) during site close-out activity.

3.11.4.5.3 Monitoring of Investigational Product Management

(a) Confirming, for the investigational product(s):

(i) That storage conditions are acceptable and in accordance with the storage requirements specified in the protocol or other relevant documents;

(ii) That supplies are sufficient throughout the trial and are used within their shelf life;

(iii) That the correct investigational product(s) are supplied only to participants who are eligible to receive it at the protocol-specified dose(s) and, where appropriate, in accordance with the randomisation procedures;

(iv) That the participants, investigator, investigator site staff and other relevant parties and individuals involved in the trial conduct are provided with necessary instruction on properly

storing, using, handling, returning and destroying, or alternative disposition of the investigational product(s);

(v) That the receipt, storage, use, handling, return and destruction or alternative disposition of the investigational product(s) are controlled and documented adequately;

(vi) That the disposition of unused investigational product(s) complies with applicable regulatory requirement(s) and is in accordance with the sponsor requirements;

(vii) Where product available on the market is dispensed and used in accordance with applicable regulatory requirements, some of the previously outlined considerations may not be applicable.

3.11.4.5.4 Monitoring of Clinical Trial Data

(a) Verifying that the investigator is enrolling only eligible trial participants.

(b) Checking the accuracy, completeness and consistency of the reported trial data against the source records and other trial-related records and whether these were reported in a timely manner. This can be done on the basis of using samples and supported by data analytics, as appropriate. The sample size and the types of data or records may need adjustment based on previous monitoring results or other indications of insufficient data quality. Monitoring should:

(i) Verify that the data required by the protocol and identified as data of higher criticality in the monitoring plan are consistent with the source;

(ii) Identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations;

(iii) Examine data trends, such as the range, consistency and variability of data within and across sites;

(c) Identifying significant errors in data collection and reporting at a site or across sites, potential data manipulation and data integrity problems.

3.11.4.6 Monitoring Report

(a) Reports of monitoring activities should include a summary of what was reviewed, a description of significant findings, conclusions and actions required to resolve them and follow-up on their resolution including those not resolved in previous reports. The requirements of monitoring reports (including their content and frequency) should be described in the sponsor's procedures.

(b) Reports of investigator site and/or centralised monitoring should be provided to the appropriate sponsor staff as described in the sponsor's procedures in a timely manner for review and follow-up.

(c) When needed, the report should describe findings requiring escalation for action and resolution. The sponsor should decide on the appropriate action to be taken, and these decisions and the resolution of the actions involved, where needed, should be recorded.

3.12 Noncompliance

3.12.1 Noncompliance with the protocol, SOPs, GCP and/or applicable regulatory requirement(s) by an investigator/institution or by member(s) of the sponsor's staff should lead to appropriate and proportionate action by the sponsor to secure compliance.

3.12.2 If noncompliance that significantly affects or has the potential to significantly affect the rights, safety or well-being of trial participant(s) or the reliability of trial results is discovered, the sponsor should perform a root cause analysis, implement appropriate corrective and preventive actions and confirm their adequacy unless otherwise justified. Where the sponsor identifies issues that are likely to significantly impact the rights, safety or well-being of the trial participant(s) or the reliability of trial results (i.e., serious noncompliance), the sponsor should notify the regulatory authority and/or IRB/IEC, in accordance with applicable regulatory requirements, and/or investigator, as appropriate.

3.12.3 If significant noncompliance is identified on the part of an investigator/institution or service provider that persists despite efforts at remediation, the sponsor should consider terminating the investigator's/institution's or service provider's participation in the trial. In these circumstances, the sponsor should promptly notify the regulatory authority(ies) and IRB/IEC of the serious noncompliance, as appropriate, and take actions to minimise the impact on the trial participants and the reliability of the results.

3.13 Safety Assessment and Reporting

The sponsor is responsible for the ongoing safety evaluation of the investigational product(s). The Investigator's Brochure or, where applicable, the current scientific information such as a basic product information brochure, forms the basis of safety assessment and reporting for the clinical trial. For further information, see Appendix A.

3.13.1 Sponsor Review of Safety Information

The sponsor should aggregate, as appropriate, and review in a timely manner relevant safety information. This includes the review of any reported unfavourable medical events occurring in participants before investigational product administration (e.g., during screening). This may result in the update of the protocol, Investigator's Brochure, informed consent materials and related documents.

The sponsor should review the available emerging safety information to assess whether there is any new data that may affect the participant's willingness to continue

in the trial, impact the conduct of the trial, or alter the approval/favourable opinion of the IRB/IEC and/or regulatory authority(ies), as applicable. Any information of this nature should be communicated to the participants, investigator, IRB/IEC and regulatory authorities, as applicable, in a timely manner.

3.13.2 Safety Reporting

(a) The sponsor should submit to the regulatory authority(ies) safety updates and periodic reports, including changes to the Investigator's Brochure, as required by applicable regulatory requirements.

(b) The sponsor should, in accordance with the applicable regulatory requirement(s) and with ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, expedite the reporting to the regulatory authority(ies) of all suspected, unexpected and serious adverse reactions (i.e., SUSARs).

(c) Safety reporting to regulatory authorities should be undertaken by assessing the expectedness of the reaction in relation to the applicable product information (e.g., the reference safety information (RSI) contained within the Investigator's Brochure or alternative documents) in accordance with applicable regulatory requirements. Refer to ICH E2F Development Safety Update Report for more information about RSI.

(d) The reporting of SUSARs to investigator(s)/institutions(s) and to the IRB(s)/IEC(s) should be undertaken in a manner that reflects the urgency of action required and should take into consideration the evolving knowledge of the safety profile of the product and should be performed in accordance with applicable regulatory requirements. In some regions, periodic reporting of line listings with an overall safety assessment may be appropriate.

(e) Urgent safety issues requiring immediate attention or action should be reported to the IRB/IEC and/or regulatory authority(ies) and investigators without undue delay and in accordance with applicable regulatory requirements.

(f) Alternative arrangements for safety reporting to regulatory authorities, IRBs/IECs and investigators and for reporting by investigators to the sponsor should be prospectively agreed upon with the regulatory authority(ies) and, if applicable, the IRB/IEC, and described in the clinical trial protocol (e.g., SAEs considered efficacy or safety endpoints, which would not be subject to unblinding and expedited reporting; see ICH E2A). See ICH E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials.

3.13.3 Managing an Immediate Hazard

The sponsor should take prompt action to address immediate hazards to participants. The sponsor should determine the causes of the hazard and based on this, take appropriate remedial actions.

The sponsor should consider whether the protocol requires amendment in response to an immediate hazard. The information on the immediate hazard, if required, and any subsequent protocol amendment should be submitted to the IRB/IEC and/or regulatory authorities by the investigator/institution or sponsor (in accordance with applicable regulatory requirements).

3.14 Insurance/Indemnification/Compensation to Participants and Investigators

3.14.1 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial except for claims that arise from malpractice and/or negligence.

3.14.2 The sponsor's policies and procedures should address the costs of treatment of trial participants in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

3.14.3 The approach to compensating trial participants should comply with applicable regulatory requirement(s).

3.15 Investigational Product(s)

3.15.1 Information on Investigational Product(s)

The sponsor should ensure that an Investigator's Brochure is developed and updated as significant new information on the investigational product becomes available. Alternatively, for authorised medicinal products, the sponsor should identify the basic product information to be used in the trial (see Appendix A, section A.1.1).

3.15.2 Manufacturing, Packaging, Labelling and Coding Investigational Product(s)

(a) The sponsor should ensure that the investigational product(s) (including active control(s) and placebo, if applicable) is characterised as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s).

(b) The sponsor should determine acceptable storage temperatures, storage conditions (e.g., protection from light) and shelf life for the investigational product(s), appropriate reconstitution fluids and procedures, and devices for product administration, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations.

(c) The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

(d) In blinded trials, the sponsor should implement:

(i) A process to blind individuals, including the sponsor staff, trial participant, investigator and/or investigator site staff, as appropriate, to the investigational product identity and assignment, and a process to prevent and detect inappropriate unblinding;

(ii) A procedure and mechanism that permits the investigator to rapidly identify the product(s) in case of a medical emergency where unblinding is considered necessary, while protecting the identity of the treatment assignment of the other trial participants;

(iii) A mechanism that protects the blinding of the trial where a participant's treatment assignment is unblinded for the purpose of safety reporting to regulatory authorities and/or IRB/IEC, where appropriate.

(e) If significant formulation changes are made in the investigational product(s) (including active control(s) and placebo, if applicable) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g., stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

3.15.3 Supplying and Handling Investigational Product(s)

(a) The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s). Where appropriate, the sponsor may supply the investigational product(s) to the trial participants in accordance with applicable regulatory requirements. Investigational product should be supplied after obtaining the required approval/favourable opinion from the IRB/IEC and the regulatory authority(ies) for the trial. Various approaches for shipping and dispensing may be undertaken, for example, by taking into consideration the characteristics of the investigational products, the route and complexity of administration and the level of existing knowledge about the investigational product's safety profile. Investigational product management should be arranged and conducted in accordance with applicable regulatory requirements, and safeguards should be in place to ensure product integrity, product use per protocol and participant safety.

(b) The sponsor should ensure that instructions are available for the investigator/institution or trial participants on the handling and storage of investigational product(s). The procedures should consider adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from participants and return of unused investigational product(s) to the sponsor (or alternative disposition if authorised by the sponsor and in compliance with the applicable regulatory requirement(s)).

(c) The sponsor should:

(i) Ensure timely provision of investigational product(s) to the investigator(s) or, where appropriate, to trial participants in accordance with applicable regulatory requirements to avoid any interruption to the trial as well as for the continuation of treatment for participants;

(ii) Maintain records that document the identity, shipment, receipt, return and destruction or alternative disposition of the investigational product(s) (see Appendix C);

(iii) Maintain a process for retrieving investigational products and documenting this retrieval (e.g., for deficient product recall, return and destruction or alternative disposition after trial completion, or expired product reclaim);

(iv) Maintain a process for the disposition of unused investigational product(s) and for the documentation of this disposition;

(v) Take steps to ensure that the investigational product(s) are stable over the period of use and only used within the current shelf life;

(vi) Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications should this become necessary and maintain records of batch sample analyses and characteristics. The samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period. The samples may not need to be kept by the sponsor in trials where an authorised medicinal product is used as an investigational product unmodified from its authorised state in accordance with local regulatory requirements. In this situation, samples are typically kept by the manufacturer.

3.16 Data and Records

3.16.1 Data Handling

(a) The sponsor should ensure the integrity and confidentiality of data generated and managed.

(b) The sponsor should apply quality control to the relevant stages of data handling to ensure that the data are of sufficient quality to generate reliable results. The sponsor should focus their quality assurance and quality control activities, including data review, on data of higher criticality and relevant metadata.

(c) The sponsor should pre-specify data to be collected and the method of its collection in the protocol (see Appendix B). Where necessary, additional details, including a data flow diagram, should be contained in a protocol-related document (e.g., a data management plan).

(d) The sponsor should ensure that data acquisition tools are fit for purpose and designed to capture the information required by the protocol. They should be validated and ready for use prior to their required use in the trial.

(e) The sponsor should ensure that documented processes are implemented to ensure the data integrity for the full data life cycle (see section 4.2).

(f) The sponsor should implement measures to ensure the safeguarding of the blinding, if any (e.g., maintain the blinding during data entry and processing).

(g) The sponsor should put procedures in place to describe unblinding, where applicable; these descriptions should include:

  (i) Who were unblinded, at what timepoint and for what purpose they were unblinded;

  (ii) Who should remain blinded;

  (iii) The safeguards in place to preserve the blinding.

(h) The sponsor should provide guidance to investigators/institutions, service providers and trial participants, where relevant, on the expectations for data capture, data changes, data retention and data disposal.

(i) The sponsor should not make changes to data entered by the investigator or trial participants unless justified, agreed upon in advance by the investigator and documented.

(j) The sponsor should allow correction of errors to data, including data entered by participants, where requested by the investigators/participants. Such data corrections should be justified and supported by source records around the time of original entry.

(k) The sponsor should ensure that the investigator has timely access to data collected in accordance with the protocol during the course of the trial, including relevant data from external sources (e.g., central laboratory data, centrally read imaging data and, if appropriate, ePRO data). This enables the investigators to make decisions (e.g., on eligibility, treatment, continuing participation in the trial and care for the safety of the individual trial participants) (see section 2.12.3). The sponsor should not share data that may unblind the investigator and should include the appropriate provisions in the protocol.

(l) The sponsor should not have exclusive control of data captured in data acquisition tools in order to prevent undetectable changes.

(m) The sponsor should ensure that the investigator has access to the required data for retention purposes.

(n) The sponsor should ensure that the investigator receives instructions on how to navigate systems, data and relevant metadata for the trial participants under their responsibility.

(o) The sponsor should seek investigator endorsement of their reported data at predetermined important milestones.

(p) The sponsor should determine the data management steps to be undertaken prior to analysis to ensure the data are of sufficient quality. These steps may vary depending on the purpose of the analysis to be conducted (e.g., data for IDMC, for interim analysis or the final analysis) (see section 4.2.6). Completion of these steps should be documented.

(q) For planned interim analysis, the ability to access and change data should be managed depending on the steps to achieve data of sufficient quality for analysis.

(r) Prior to provision of the data for final analysis and, where applicable, before unblinding the trial, edit access to the data acquisition tools should be restricted.

(s) The sponsor should use an unambiguous trial participant identification code that allows identification of all the data reported for each participant.

(t) The sponsor should implement appropriate measures to protect the privacy and confidentiality of personal information of trial participants, in accordance with applicable regulatory requirements on personal data protection.

(u) In accordance with applicable regulatory requirements and in alignment with the protocol, the sponsor should describe the process by which the participant's data will be handled when a participant withdraws or is discontinued from the trial.

(v) The sponsor should ensure that trial data are protected from unauthorised access, disclosure, dissemination or alteration and from inappropriate destruction or accidental loss.

(w) The sponsor should have processes and procedures in place for reporting to relevant parties, including regulatory authorities, incidents (including security breaches) that have a significant impact on the trial data.

(x) When using computerised systems in a clinical trial, the sponsor should:

For systems deployed by the sponsor:

(i) Have a record of the important computerised systems used in a clinical trial. This should include the use, functionality, interfaces and validation status of each computerised system, and who is responsible for its management should be described. The record should also

include a description of implemented access controls and internal and external security measures;

(ii) Ensure that the requirements for computerised systems (e.g., requirements for validation, audit trails, user management, backup, disaster recovery and IT security) are addressed and implemented and that documented procedures and adequate training are in place to ensure the correct development, maintenance and use of computerised systems in clinical trials (see section 4). These requirements should be proportionate to the importance of the computerised system and the data or activities they are expected to process;

(iii) Maintain a record of the individual users who are authorised to access the system, their roles and their access permissions;

(iv) Ensure that access permissions granted to investigator site staff are in accordance with delegations by the investigator and visible to the investigator;

(v) Ensure that there is a process in place for service providers and investigators to inform the sponsor of system defects identified;

For systems used or deployed by the investigator/institution:

(vi) Assess whether such systems, if identified as containing source records in the trial, (e.g., electronic health records, other record keeping systems for source data collection and investigator site files) are fit for purpose or whether the risks from a known issue(s) can be appropriately mitigated. This assessment should occur during the process of selecting clinical trial sites and should be documented;

(vii) In situations where clinical practice computerised systems are being considered for use in clinical trials (e.g., electronic health records or imaging systems used or deployed by the investigator/institution), these systems should be assessed for their fitness for purpose in the context of the trial;

(viii) The assessment should be performed before being used in the trial and should be proportionate to the importance of the data managed in the system. Factors such as data security (including measures for backup), user management and audit trails, which help ensure the protection of confidentiality and integrity of the trial data, should be considered as appropriate;

For all systems:

(ix) Ensure that there is a process in place for service providers and investigator(s)/institution(s) to inform the sponsor of incidents that could potentially constitute a serious noncompliance with the clinical

trial protocol, trial procedures, applicable regulatory requirements or GCP in accordance with section 3.12.

3.16.2 Statistical Programming and Data Analysis

This section concerning documentation of operational aspects of clinical trial statistical activities should be read in conjunction with ICH E9 Statistical Principles for Clinical Trials and ICH E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to The Guideline on Statistical Principles for Clinical Trials, which provides detailed guidance on statistical principles for clinical development, trial design, conduct, analysis and reporting.

(a) The sponsor should develop a statistical analysis plan that is consistent with the trial protocol and that details the approach to data analysis, unless the approach to data analysis is sufficiently described in the protocol.

(b) The sponsor should ensure that appropriate and documented quality control of statistical programming and data analysis is implemented (e.g., for sample size calculations, analysis results for IDMC review, outputs for clinical trial report, statistical or centralised monitoring).

(c) The sponsor should ensure the traceability of data transformations and derivations during data processing and analysis.

(d) The sponsor should ensure that the criteria for inclusion or exclusion of trial participants from any analysis set is pre-defined (e.g., in the protocol or the statistical analysis plan). The rationale for exclusion for any participant (or particular data point) should be clearly described and documented.

(e) Deviations from the planned statistical analysis or changes made to the data after the trial has been unblinded (where applicable) should be clearly documented and justified and should only occur in exceptional circumstances (e.g., data discrepancies that must be resolved for the reliability of the trial results). Such data changes should be authorised by the investigator and reflected in an audit trail. Post-unblinding data changes and deviations from the planned statistical analyses should be reported in the clinical trial report.

(f) The sponsor should retain the statistical programming records that relate to the output contained or used in reports of the trial results, including quality control/validation activities performed. Outputs should be traceable to the statistical software programs, dated and time stamped, protected against any changes, and have access controls implemented to avoid inappropriate viewing of information that may introduce bias.

3.16.3 Record Keeping and Retention

(a) The sponsor (or subsequent owners of the data) should retain the sponsor-specific essential records pertaining to the trial in accordance with the applicable regulatory requirement(s) (see Appendix C).

(b) The sponsor should inform the investigator(s)/institution(s) and service providers, when appropriate, in writing of the requirements for the retention of essential records and should notify the investigator(s)/institution(s) and service providers, when appropriate, in writing when the trial-related records are no longer needed in accordance with applicable regulatory requirements.

(c) The sponsor should report to the appropriate authority(ies) any transfer of ownership of the essential records as required by the applicable regulatory requirement(s). The sponsor should also inform the investigator if sponsorship of the trial changes.

3.16.4 Record Access

(a) The sponsor should ensure that it is specified in the protocol or other documented agreement that the investigator(s)/institution(s) provide direct access to source records for trial-related monitoring, audits, regulatory inspection and, in accordance with applicable regulatory requirements, IRB/IEC review.

(b) The sponsor should ensure that trial participants have consented to direct access to source records for the purposes outlined in 3.16.4(a) (see section 2.8.10(o)).

3.17 Reports

3.17.1 Premature Termination or Suspension of a Trial

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided with the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, in accordance with applicable regulatory requirement(s). Where appropriate, the sponsor should provide the investigator with information about potential subsequent therapy(ies) and follow-up for the participants.

3.17.2 Clinical Trial/Study Reports

(a) Whether the trial is completed or prematurely terminated, or an interim analysis is undertaken for regulatory submission, the sponsor should ensure that the clinical trial reports, including interim reports, are prepared and provided to the regulatory authority(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of ICH E3 or are otherwise in accordance with applicable regulatory requirements. (Note: ICH E3 specifies that abbreviated trial reports may be acceptable in certain cases.)

(b) Where a coordinating investigator is involved in a trial, consideration should be given to them being a signatory on the clinical trial report (see ICH E3).

(c) Once the trial has been unblinded and relevant analyses/conclusions have been completed and finalised, the sponsor should generally, in accordance with applicable regulatory requirements:

(i) Make trial results publicly available;

(ii) Provide the investigator with information about the treatment taken by their participants for blinded trials;

(iii) Provide investigators with the trial results. Where a summary of trial results is provided to participants, this should have language that is non-technical, understandable to a layperson and non-promotional.

4. DATA GOVERNANCE – INVESTIGATOR AND SPONSOR

This section provides guidance to the responsible parties (i.e., investigators and sponsors) on appropriate management of data integrity, traceability and security, thereby allowing the accurate reporting, verification and interpretation of the clinical trial-related information. This section should be read in conjunction with corresponding responsibilities for the investigator and the sponsor as defined in sections 2 and 3, along with ICH E8(R1), ICH E9 and ICH E9(R1).

The quality and amount of the information generated in a clinical trial should be sufficient to address trial objectives, provide confidence in the trial's results and support good decision making.

The systems and processes that help ensure this quality should be designed and implemented in a way that is proportionate to the risks to participants and the reliability of trial results.

The following key processes should address the full data life cycle with a focus on the criticality of the data and should be implemented proportionately and documented appropriately:

(a) Processes to ensure the protection of the confidentiality of trial participants' data;

(b) Processes for managing computerised systems to ensure that they are fit for purpose and used appropriately;

(c) Processes to safeguard essential elements of the clinical trial, such as randomisation, dose adjustments and blinding;

(d) Processes to support key decision making, such as data finalisation prior to analysis, unblinding, allocation to analysis data sets, changes in clinical trial design and, where applicable, the activities of, for example, an IDMC.

4.1 Safeguard Blinding in Data Governance

4.1.1 Maintaining the integrity of the blinding is important in particular in the design of systems, management of users' accounts, delegation of responsibilities with respect

to data handling and provision of data access at sites, data transfers, database review prior to planned unblinding and statistical analysis across all appropriate stages of the trial.

4.1.2 Roles, responsibilities and procedures for access to unblinded information should be defined and documented by all relevant parties according to the protocol; this information may also be included in the data management plans and statistical analysis plans or other trial specific plans/instructions and site staff delegation records. For example, in blinded trials, sponsor staff or service providers who are involved in operation of the trial and directly or indirectly interact with investigator site staff should not have access to unblinding information except when justified by the trial design (e.g., use of unblinded monitors).

4.1.3 In such cases, suitable mitigation strategies should be implemented to reduce the risk of inadvertent unblinding of the blinded investigator site staff.

4.1.4 The potential for unblinding should be part of the risk assessment of a blinded trial. Any planned or unplanned unblinding, including inadvertent or emergency unblinding, should be documented. Any unplanned unblinding should be assessed for its impact on the trial results, and actions should be taken as appropriate.

4.2 Data Life Cycle Elements

Procedures should be in place to cover the full data life cycle.

4.2.1 Data Capture

(a) When data captured on paper or in an electronic health record are manually transcribed into a computerised system (e.g., data acquisition tool), the need for and the extent of data verification should take the criticality of the data into account.

(b) Acquired data from any source, including data directly captured in a computerised system (e.g., data acquisition tool), should be accompanied by relevant metadata.

(c) At the point of data capture, automated data validation checks to raise data queries should be considered as required based on risk, and their implementation should be controlled and documented.

4.2.2 Relevant Metadata, Including Audit Trails

The approach used by the responsible party for implementing, evaluating, accessing, managing and reviewing relevant metadata associated with data of higher criticality should entail:

(a) Evaluating the system for the types and content of metadata available to ensure that:

(i) Computerised systems maintain logs of user account creation, changes to user roles and permissions and user access;

(ii) Systems are designed to permit data changes in such a way that the initial data entry and any subsequent changes or deletions are documented, including, where appropriate, the reason for the change;

(iii) Systems record and maintain workflow actions in addition to direct data entry/changes into the system.

(b) Ensuring that audit trails, reports and logs are not disabled. Audit trails should not be modified except in rare circumstances (e.g., when a participant's personal information is inadvertently included in the data) and only if a log of such action and justification is maintained;

(c) Ensuring that audit trails and logs are interpretable and can support review;

(d) Ensuring that the automatic capture of date and time of data entries or transfer are unambiguous (e.g., coordinated universal time (UTC));

(e) Determining which of the identified metadata require review and retention.

4.2.3 Review of Data and Metadata

Procedures for review of trial-specific data, audit trails and other relevant metadata should be in place. It should be a planned activity, and the extent and nature should be risk-based, adapted to the individual trial and adjusted based on experience during the trial.

4.2.4 Data Corrections

There should be processes to correct data errors that could impact the reliability of the trial results. Corrections should be attributed to the person or computerised system making the correction, justified and supported by source records around the time of original entry and performed in a timely manner.

4.2.5 Data Transfer, Exchange and Migration

Validated processes and/or other appropriate processes such as reconciliation should be in place to ensure that electronic data, including relevant metadata, transferred between computerised systems retains its integrity and preserves its confidentiality. The data exchange/transfer process or system migration should be documented to ensure traceability, and data reconciliation should be implemented as appropriate to avoid data loss and unintended modifications.

4.2.6 Finalisation of Data Sets Prior to Analysis

(a) Data of sufficient quality for interim and final analysis should be defined and are achieved by implementing timely and reliable processes for data capture, verification, validation, review and rectification of errors and, where possible,

omissions that have a meaningful impact on the safety of trial participants and/or the reliability of the trial results.

(b) Activities undertaken to finalise the data sets prior to analysis should be confirmed and documented in accordance with pre-specified procedures. These activities may include reconciliation of entered data and data sets or reconciliation of relevant databases, rectification of data errors and, where possible, omissions, medical coding and compilation of and addressing the impact of noncompliance issues, including protocol deviations.

(c) Data extraction and determination of data analysis sets should take place in accordance with the planned statistical analysis and should be documented.

4.2.7 Retention and Access

The trial data and relevant metadata should be archived in a way that allows for their retrieval and readability and should be protected from unauthorised access and alterations throughout the retention period.

4.2.8 Destruction

The trial data and metadata may be permanently destroyed when no longer required as determined by applicable regulatory requirements.

4.3 Computerised Systems

As described in sections 2 and 3, the responsibilities of the sponsor, investigator and the activities of other parties with respect to a computerised system used in clinical trials should be clear and documented.

The responsible party should ensure that those developing computerised systems for clinical trials on their behalf are aware of the intended purpose and the regulatory requirements that apply to them.

It is recommended that representatives of intended participant populations and healthcare professionals are involved in the design of the system, where relevant, to ensure that computerised systems are suitable for use by the intended user population.

4.3.1 Procedures for the Use of Computerised Systems

Documented procedures should be in place to ensure the appropriate use of computerised systems in clinical trials for essential activities related to data collection, handling and management.

4.3.2 Training

The responsible party should ensure that those using computerised systems are appropriately trained in their use.

4.3.3 Security

(a) The security of the trial data and records should be managed throughout the data life cycle.

(b) The responsible party should ensure that security controls are implemented and maintained for computerised systems. These controls should include user management and ongoing measures to prevent, detect and/or mitigate security breaches. Aspects such as user authentication requirements and password management, firewall settings, antivirus software, security patching, system monitoring and penetration testing should be considered.

(c) The responsible party should maintain adequate backup of the data.

(d) Procedures should cover the following: system security measures, data backup and disaster recovery to ensure that unauthorised access and data loss are prevented. Such measures should be periodically tested, as appropriate.

4.3.4 Validation

(a) The responsible party is responsible for the validation status of the system throughout its life cycle. The approach to validation of computerised systems should be based on a risk assessment that considers the intended use of the system; the purpose and importance of the data/record that are collected/generated, maintained and retained in the system; and the potential of the system to affect the well-being, rights and safety of trial participants and the reliability of trial results.

(b) Validation should demonstrate that the system conforms to the established requirements for completeness, accuracy and reliability and that its performance is consistent with its intended purpose.

(c) Systems should be appropriately validated prior to use. Subsequent changes to the system should be validated based on risk and should consider both previously collected and new data in line with change control procedures.

(d) Periodic review may be appropriate to ensure that computerised systems remain in a validated state throughout the life cycle of the system.

(e) Both standard system functionality and protocol-specific configurations and customisations, including automated data entry checks and calculations, should be validated. Interfaces between systems should also be defined and validated. Different degrees of validation may be needed for bespoke systems, systems designed to be configured or systems where no alterations are needed.

(f) Where relevant, validation procedures (until decommissioning) should cover the following: system design, system requirement, functionality testing, configuration, release, setup, installation and change control.

(g) The responsible party should ensure that the computerised systems are validated as fit for purpose for use in the trial, including those developed by other parties. They should ensure that validation documentation is maintained and retained.

(h) Validation should generally include defining the requirements and specifications for the system and their testing, along with the associated documentation, to ensure the system is fit for purpose for use in the trial, especially for critical functionality, such as randomisation, dosing and dose titrations and reductions, and collection of endpoint data.

(i) Unresolved issues, if any, should be justified and, where relevant, the risks identified from such issues should be addressed by mitigation strategies prior to and/or during the continued use of the system.

4.3.5 System Release

The trial-specific systems (including updates resulting from protocol amendments) should only be implemented, released or activated for individual investigator sites after all necessary approvals for the clinical trial relevant to that investigator site have been received.

4.3.6 System Failure

Contingency procedures should be in place to prevent loss or lack of accessibility to data essential to participant safety, trial decisions or trial outcomes.

4.3.7 Technical Support

(a) Where appropriate, there should be mechanisms (e.g., help desk support) in place to document, evaluate and manage issues with the computerised systems (e.g., raised by users), and there should be periodic review of these cumulative issues to identify those that are repeated and/or systemic.

(b) Defects and issues should be resolved according to their criticality. Issues with high criticality should be resolved in a timely manner.

4.3.8 User Management

(a) Access controls are integral to computerised systems used in clinical trials to limit system access to authorised users and to ensure attributability to an individual. The security measures should be selected in such a way that they achieve the intended security.

(b) Procedures should be in place to ensure that user access permissions are appropriately assigned based on a user's duties and functions, blinding arrangements and the organisation to which users belong. Access permissions should be revoked when they are no longer needed. A process should be in

place to ensure that user access and assigned roles and permissions are periodically reviewed, where relevant.

(c) Authorised users and access permissions should be clearly documented, maintained and retained. These records should include any updates to a user's roles, access permissions and time of access permission being granted (e.g., time stamp).

IV. ANNEX 2

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, design elements and data sources are used in a clinical trial. For simplicity, various operational approaches, design elements and data sources are collectively referred to in this guideline also as methodologies. As clinical trial designs evolve and technological advances occur, the application of GCP should be tailored to the trial design and technologies utilised. In this context, the application of a proportionate risk-based approach (as explained in the Principles and Annex 1) remains relevant and supports the use of evolving trial designs and technologies without compromising the rights, safety and well-being of the participants and the reliability of the trial results. In response to the increased use of various operational approaches, design elements and data sources, ICH E6(R3) Annex 2 provides additional GCP considerations, focusing on trials that incorporate decentralised elements, pragmatic elements and/or real-world data (RWD). Clinical trials may incorporate one or more of these methodologies. Annex 2 is not meant to be comprehensive of all methodologies, recognising that clinical trial ecosystems may continue to evolve, and new approaches, designs and data types may emerge. Considerations included in this Annex may be applied to those evolving methodologies provided they are applied in accordance with local regulatory requirements. This Annex should not be read as an endorsement of any specific methodologies 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. These may include trial visits and/or protocol-related procedures conducted at the trial participant's home, local healthcare centres or mobile medical units. They also encompass remote interactions, such as video calls or the use of digital health technologies (DHTs) to conduct visits, perform procedures and collect data.

In Annex 2, the term DHTs is used as a broad term to reflect the wide range of technologies supporting healthcare used to collect, measure, or monitor health-related data from participants or patients (e.g., mobile applications, wearables, and sensors). Depending on the context, the term may refer to those technologies used specifically in trials or those used within broader healthcare settings. Where a DHT is used to acquire participant data for a clinical trial, it is considered a data acquisition tool (as defined in the Glossary).

Pragmatic elements in clinical trials are those that integrate aspects of usual clinical practice into the design and conduct of the trial. Usual clinical practice refers to the established day-to-day processes and procedures applied by healthcare professionals when caring for patients. Such elements may include protocols with trial processes and eligibility criteria that reflect usual clinical practice in that patient population and reflect the settings where usual care is provided, such as in hospitals, in healthcare centres and by primary physicians and/or local healthcare providers. Pragmatic elements also include streamlined data collection, for example, capturing only the minimum necessary data by aligning with usual clinical practice or capturing data only at the timing in routine care settings to minimise the complexity of trial conduct. Technologies, such as DHTs, and automated data exports from electronic health records (EHRs) can be used to help such streamlined data collection.

RWD incorporated in interventional clinical trials refers to the use of data relating to patient health status collected from a variety of sources outside of clinical trials (e.g., EHRs, registries, claims databases).

In the context of clinical trials, data are often used in one of two ways: as primary data collection, when collected specifically for the trial, or as secondary use, when repurposed from existing sources collected for other purposes. Both types of data use can contribute meaningfully to trial objectives, but each requires different considerations for data quality, data governance and regulatory acceptability.

Primary data collection involves gathering data prospectively in accordance with the trial protocol, typically through trial-specific procedures such as clinical assessments, laboratory tests or participant questionnaires. Secondary use of data refers to the use of data originally collected for purposes other than the clinical trial but are subsequently incorporated into that clinical trial. When such data reflects patient experiences, outcomes or healthcare delivery outside a clinical trial setting, it is considered RWD. These data can serve various roles in a trial, including but not limited to endpoint or outcome data or serving as an external control. When such data are used in a trial, it is essential to ensure that the data are fit for their intended purpose in the clinical trial.

As stated in the Principles and Annex 1, a quality by design (QbD) approach should be used in clinical trials to ensure that the methodologies adopted and implemented are fit for purpose and the quality and amount of information generated or collected is sufficient to support good decision making. When planning and implementing decentralised and pragmatic elements in clinical trials, it is important to consider the needs of the participants. These include the availability of, and familiarity with, the use of technologies as well as whether there is any burden to participants that needs to be balanced with the use of such elements.

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 to, for example, measures to ensure participants' rights, safety and well-being, to protect their privacy and confidentiality and to secure their data.

2. INVESTIGATOR

2.1 Communication with IRB/IEC

The investigator, in accordance with applicable regulatory requirements, should provide the IRB/IEC with the information needed for the evaluation of the appropriateness of the methodologies being used (see Annex 1, sections 1.1 and 2.4).

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 for providing information to the participant (or legally acceptable representative, where applicable) and for supporting the participant's understanding of the trial (see Annex 1, section 2.8). The informed consent process, including the methods and tools described below for obtaining consent, should be in accordance with applicable regulatory requirements. The informed consent materials and process should be tailored to reflect the various operational approaches, design elements and data sources incorporated in the trial.

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). This may be performed, for example, by verification of an official identification document via a video call. The verification method along with the measures to safeguard data privacy should be pre-specified.

2.2.2 The characteristics of the trial population (e.g., participants may lack familiarity with computerised 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. When computerised systems are used to support the informed consent process and/or when informed consent is obtained remotely, 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 participant-related data will be collected, how the data may be used in the trial and which parties 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.

2.3.1 The investigator/institution may arrange to send the investigational product to the participant (e.g., to the participant's home) following the sponsor's documented instructions, where applicable. Such arrangements should also comply 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 (i.e., 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 Where permitted by applicable regulatory requirements, the sponsor may arrange to send the investigational product to the participant. In such cases:

(a) The investigator/institution retains responsibility for the safe and appropriate use of the investigational product for participants under their care.

(b) The investigator should be aware of the arrangements for shipping the investigational product to participants from the sponsor and remain informed of the investigational product receipt, use and any participant-reported issues and their resolution.

(c) There should be clear documentation of the roles and responsibilities of the sponsor and the investigator.

(d) There should be clear communication and predefined procedures between the sponsor, the investigator and any service provider involved in the shipping of the investigational product.

2.3.3 Certain documentation and processes already used in the institution/healthcare centre may be sufficient for the management of the investigational product, depending on applicable 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.

2.3.4 The investigator should maintain appropriate oversight of the activities related to investigational product management and should ensure that appropriate documentation is maintained (see Annex 1, section 2.10.4). The level of investigator oversight will depend on a number of factors, including the trial design, 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). The activities that should be under the oversight of the investigator 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.

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

2.4 Investigator Oversight

The investigator should maintain appropriate and proportionate oversight of trial-related activities to ensure the rights, safety and well-being of the trial participants and the reliability of trial data.

The level of investigator oversight should depend on the nature of the trial-related activities and should be proportionate to the importance of the data being collected and the risk to trial participant rights, safety and well-being and data reliability.

An appropriate level of oversight is context-dependent (e.g., depending on trial characteristics, such as trial design, trial population, investigational product and data sources). An appropriate level of oversight may range from direct supervision to less intensive oversight, whether in person or via remote communication methods (e.g., video, telephone or email), to only the review of essential records (including source records).

2.4.1. Investigator Oversight of Healthcare Professionals Conducting Trial Activities Within Usual Clinical Practice

Healthcare professionals may be involved in performing trial-related activities that are part of usual clinical practice. In such cases, the protocol should describe these trial-related activities to be performed by these healthcare professionals (see Annex 2, section 3.2.2).

For trial-related activities that are part of usual clinical practice, conducted by healthcare professionals, and which do not require knowledge about the protocol, investigator's brochure or other trial-related documents (e.g., manuals describing trial-specific procedures), appropriate arrangements should be in place. Such arrangements should address plans for making relevant information and records on the performed trial-related activities available to the investigator. These include defining how data are shared, how records are retained (e.g., certified copy), how data privacy is maintained and what mechanisms are in place for ensuring data integrity.

Where trial-related activities are part of usual clinical practice and knowledge of the protocol, investigator's brochure or other trial-related document is required, delegated healthcare professionals who have been appropriately trained should perform these activities (see Annex 1, section 2.3.1).

In either case mentioned above, the level of investigator oversight should be proportionate to the criticality of data to participant protection and the reliability of the trial results. Regardless of whether healthcare professionals involved in the trial are arranged by the sponsor or investigator, such oversight should ensure that the resulting records meet the relevant requirements of the protocol and thereby ensure reliable trial results, trial participant protection 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. Safety information generated from, for example, home nursing, remote visits, and use of DHTs, should be provided to the investigator in a manner that allows the investigator to make decisions on the care of the participant and ensures participant safety (see Annex 2, section 3.9 and Annex 1, section 3.13.2).

3. SPONSOR

3.1 Engagement and Communication

Engagement with relevant interested parties is particularly important when utilising various methodologies in clinical trials. Their early involvement may be valuable in refining research questions; selecting meaningful interventions and outcomes; and shaping trial design, procedures and communication strategies. The following considerations are important in communicating with relevant interested parties and may be undertaken in various ways, taking into account ICH E8(R1) General Considerations for Clinical Studies (see also Annex 1, section 3.1.3).

3.1.1 Engaging patients, patient advocacy groups and their communities, as appropriate, can help ensure the successful integration and implementation of the methodologies used in trials. For example, involving patients early in the design of the trial may help to refine the trial design, including ensuring the suitability of DHTs (e.g., mobile applications, wearables) used in trials with decentralised elements, and help address issues related to the logistics of participation. This engagement may also highlight

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 methodologies 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 usual clinical practice of healthcare professionals, when appropriate, and that allow for the integration of data generated from usual clinical practice when such data are fit for purpose.

(c) Identify areas where training or support is needed.

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

3.2 Protocol and Trial Design

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 protocol-related documents when utilising various methodologies so that all parties involved in the trial conduct are adequately informed.

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

3.2.2 Sponsors considering incorporating trial-related activities that are part of usual clinical practice (i.e., pragmatic elements) should assess whether such an approach is fit for purpose for use in the trial and complies with applicable regulatory requirements. Where such activities are incorporated in the trial, sponsors should ensure that the protocol clearly describes how, by whom, and under what circumstances these trial-related activities will be performed to ensure these activities are well understood and appropriately implemented (see Annex 2, section 2.4.1).

3.2.3 Since data may originate from different sources or practice settings (e.g., sources with different data collection timings), there may be data variability within and/or between data sources or 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).

3.2.4 The methodologies used in the trial should be considered when determining the need for appropriate training and technical support to be provided to the investigator, investigator site staff and participants.

3.2.5 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 data and information suggesting a potential safety

concern will be identified and made available to the investigator in a timely manner, 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 Annex 2, sections 2.5 and 3.9).

3.2.6 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 applicable regulatory requirements, should ensure that the IRB/IEC is provided with the information needed to evaluate the appropriateness of the methodologies being used (see Annex 1, sections 1.1 and 3.8.2).

3.4 Access to and Use of RWD

Sponsors are ultimately responsible for ensuring that RWD used in a clinical trial are managed in a manner that ensures participant protection and the reliability of trial results. This includes ensuring that the data are fit for purpose, that appropriate access and oversight are in place, and that use of such data complies with applicable privacy and data protection requirements, including consent and permission.

3.4.1. Access to RWD

Sponsors are responsible for ensuring that RWD used in a clinical trial are fit for purpose (i.e., they are relevant and reliable; see Annex 2, section 3.5.1) and ultimately support the reliability of the trial results. To fulfil this responsibility, sponsors should have the ability to access individual-level data, whether generated by themselves or by other entities (including service providers), and data in source records as necessary in accordance with applicable regulatory requirements. Sponsor access to such data may be necessary, for example, to implement quality assurance and control. For regulatory inspection purposes, regulatory authorities may require access to individual-level data and data in source records in accordance with applicable regulatory requirements.

Individual-level data (pseudonymised for trial use) are datasets or listings capturing data for each individual, usually extracted from source records and structured for statistical analysis and reporting. Pseudonymised data are processed such that a specific individual cannot be identified without collating the data with additional information. Data in source records refer to the data in the original records, such as patient medical records, laboratory reports, imaging files and physician notes, from which individual-level data are derived (see the glossary term “source records”). Source records are typically not pseudonymised and contain patient-identifying information as well as other information subject to data privacy and protection requirements.

RWD used in a clinical trial may be owned and controlled by entities other than the sponsor (e.g., healthcare institutions, registry holders, insurers). In such cases, the sponsor should ensure appropriate arrangements are in place with these entities to enable access and use of the data for trial purposes. This should include access to data in source records by the sponsor for the purpose of quality assurance and quality control in accordance with applicable regulatory requirements. The arrangements

should also allow regulatory authorities to access individual-level data and source records to support regulatory inspections.

These arrangements should include documented agreements that define how data will be shared and protected in accordance with applicable regulatory requirements as well as the institutional policies of each party.

The extent of sponsor access to individual-level data and data in source records should be proportionate to the criticality of the data (see Annex 1, section 3.16.1(b)). For RWD use cases of higher criticality (e.g., when RWD are used to support key efficacy and safety endpoints), simply assessing the fitness for purpose of the RWD source to be utilised (see Annex 2, section 3.5.1(b)) may be insufficient to ensure reliability of the data. Therefore, it may be necessary for the sponsors for example to confirm whether a clinical event occurred, was assessed, or was documented. In such cases, sponsors should ensure access to source records to support their quality assurance and quality control activities. Where such access is not feasible due to constraints set by entities who own and/or control the RWD, sponsors should consult relevant regulatory authorities. For RWD use cases of lower criticality (e.g., for exploratory endpoints), it may be sufficient for sponsors to use system- and process-level assessments. In this case, the protocol or protocol-related documents should describe the fitness for purpose of the RWD, including any relevant limitations and justification of the assessment approach.

Regardless of which entity owns and/or controls data or undertakes data processing steps, sponsors remain responsible for oversight of these steps, including extraction, linkage and transformation, and for implementing quality assurance and quality control measures to ensure data are of appropriate quality.

3.4.2. Consent and Permission Considerations for RWD

In accordance with applicable regulatory requirements, the sponsor should ensure that permission or approval is obtained from authorised entities (e.g., IRBs/IECs) or consent is provided by individuals whose health data or source records are used to obtain RWD. The consent should describe use of and access to the RWD and their source records by regulatory authorities, and where applicable, sponsor representatives and IRBs/IECs. Such consent does not imply participation in an interventional trial-related activity. When RWD originate from data previously collected for purposes not specific to that trial and that are subsequently incorporated into the trial (i.e., secondary use of data), the way of obtaining consent may depend on the local regulatory requirements and the identifiability of the individual whose data are being used. In some regions, consent may be obtained in a broad manner to allow for potential future research use (i.e., broad consent). In other regions, permission from an IRB/IEC may substitute for obtaining consent for secondary use of data.

Sponsors should ensure that records of the consents or permissions are retained and available to regulatory authorities upon request.

3.5 Data Considerations

This section provides aspects that should be taken into consideration when utilising a variety of data sources. It should be read in conjunction with Annex 1, section 3.16.1 and section 4, Data Governance – Investigator and Sponsor.

3.5.1 RWD Considerations

(a) 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, provenance 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. Attention should be given to the variability in data source, potential bias, generalisability and traceability of RWD. The sponsor should implement procedures that support adequate documentation, data linkage and quality control, while accounting for differences in how RWD are structured, collected and managed across various sources. In selecting RWD sources, sponsors should assess whether the data are appropriate to support the specific trial endpoints and objectives and should weigh the potential benefits against limitations, taking into account the considerations described in 3.5.1(b) below. These considerations should be reflected in trial planning, protocol design and oversight processes.

(b) A variety of RWD sources may be used in clinical trials, including EHRs, administrative claims data, and registries. Since these data are typically generated outside the clinical trial, sponsors generally do not have control over how the data were originally collected, recorded, or curated.

Sponsors should assess whether the RWD source is fit for purpose for the intended use in the trial. In doing so, sponsors should also apply a risk-proportionate approach to the measures used to ensure appropriate data quality, integrity, and governance for the RWD incorporated into the trial. This approach should consider the importance of the data to the trial objectives and the potential impact of data limitations on trial results.
The considerations that may inform the determination of whether a given RWD source is fit for purpose include, but are not limited to, the following:

(i) The potential variability of data formats and structure (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) Comparability between data from the clinical trial and the control group using RWD, such as comparability of baseline factors, minimisation of potential selection bias through pre-planned patient selection, and consistency in clinical evaluation methods.

(iv) Missing data (e.g., due to participants moving to different healthcare systems) or the occurrence of intercurrent events 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.

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

(vi) De-identification methodologies (e.g., pseudonymisation) used to protect the privacy and confidentiality of personal information.

(vii) The fitness for purpose assessment of systems and tools used for the collection and acquisition of RWD (e.g., registries, DHTs), including the validation status as appropriate.

(c) Multiple data sources might need to be linked to support the reliability, including completeness 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 the reliability of trial results. If data are to be linked, this should be pre-specified in the protocol or protocol-related documents, including how data inconsistencies between different sources will be resolved in a systematic and consistent manner.

3.5.2 Remote Data Collection Considerations

(a) Remote data collection in clinical trials (e.g., the use of remote visits and DHTs, 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 Annex 2, section 3.7).

(b) Some of the RWD considerations in Annex 2, section 3.5.1 may also apply to remote clinical trial data collection.

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 and in accordance with applicable regulatory requirements (see Annex 2, sections 2.3 and 3.8; 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. Such shipment should be carried out in accordance with the protocol, and the sponsor should ensure that the shipment process is initiated after being authorised by the investigator. For specific considerations for investigational product shipping to the participant, see Annex 2, section 2.3.1; in addition, see the privacy and confidentiality considerations in Annex 2, section 3.7.

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 that security safeguards, including cybersecurity, are in place so that the privacy and confidentiality of the personal information of trial participants are protected in accordance with applicable regulatory requirements. 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, for example, when data from DHTs and/or RWD are used.

3.8 Sponsor Oversight

Sponsor oversight may be more complex depending on the wide range of methodological approaches to the trial design and conduct, and the number of service providers involved in the trial conduct. Sponsors should ensure that there are processes in place, including clear lines of communication, to provide an appropriate level of oversight such that the participants' rights, safety and well-being are protected, and the reliability of the trial results is ensured. Sponsor oversight also involves, but is not limited to, the implementation of quality control and assurance measures specifically customised to the clinical trial and its critical to quality factors and identified risks. These measures should be implemented in a manner which is proportionate to the potential impact on the protection of participants and/or the reliability of the trial results. Sponsors should maintain appropriate oversight of service providers including ensuring maintenance of their essential records (see Annex 1, sections 3.9, 3.10 and 3.11, and Appendix C).

When a sponsor arranges trial-related activities which are under the responsibility of the investigator (e.g., home nursing), the sponsor should ensure that the service providers are suitable to conduct this activity (see Annex 1, section 3.6.5). In such circumstances, the investigator retains the ability to make the decision on the appropriateness of the proposed service provider and is responsible for the oversight of their activities (see Annex 1, section 2.3.1).

3.9 Safety Assessment and Reporting

The management of safety information is an essential part of clinical trials to protect trial participants' safety through early detection and management of potential adverse drug reactions (see Annex 1, section 3.13).

3.9.1 Safety information may be collected in various ways and from multiple sources in clinical trials with decentralised and/or pragmatic elements. For example, safety information may be obtained through remote visits, DHTs, EHRs, in-person visits or a combination of these approaches. In these circumstances, the sponsor should ensure that appropriate processes and procedures are in place to make this information accessible to the investigator in a timely manner according to the protocol. The safety information should be provided to the investigator in a manner that allows the investigator to make decisions on care of the participant and ensures their safety. For example, when DHTs are used to collect data, the sponsor should ensure that

information will be provided to the investigator in a way that is relevant, meaningful and manageable, enabling an effective overview of the participant's health status and timely, appropriate medical decisions.

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 (e.g., the safety management plan). This approach should take into account the methodologies used in the trial. 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.

APPENDICES

Appendix A. INVESTIGATOR'S BROCHURE

A.1 Introduction

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s)[1] that are relevant to the study of the product(s) in human participants. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for and their compliance with many key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures.

A.1.1 Development of the Investigator's Brochure

Generally, the sponsor is responsible for ensuring that an up-to-date IB is developed. In the case of an investigator-initiated trial, the sponsor-investigator should determine whether a brochure is available from the product license/marketing authorisation holder. If the investigational product is provided by the sponsor-investigator, then they should provide the necessary information to the investigator site staff. Where permitted by regulatory authorities, the current scientific information such as a basic product information brochure (e.g., summary of product characteristics, package leaflet, or labelling) may be an appropriate alternative, provided that it includes current, comprehensive and detailed information on all aspects of the investigational product that might be of importance to the investigator. If an authorised medicinal product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared unless there is a rationale for only one IB. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's documented procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. Relevant new information may be so important that it needs to be communicated to the investigators and possibly to the institutional review boards/independent ethics committees (IRBs/IECs) and/or regulatory authorities before it is included in a revised IB.

A.1.2 Reference Safety Information and Risk-Benefit Assessment

The reference safety information (RSI) contained in the IB provides an important reference point for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) in the clinical trial. This RSI should include a list of adverse reactions, including information on their frequency and nature. This list should be used for determining the expectedness of a suspected serious adverse reaction and subsequently whether reporting needs to be expedited in accordance with applicable regulatory requirements (see Annex 1, section 3.13.2(c)).

The IB also provides insight to support the clinical management of the participants during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician

[1] For the purpose of this guideline, the term investigational products should be considered synonymous with drugs, medicines, medicinal products, vaccines and biological products.

or potential investigator to understand it and make their own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should be involved in the generation of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

A.2 General Considerations

These considerations delineate the minimum information that should be included in an IB. It is expected that the type and extent of information available will vary with the stage of development of the investigational product.

The IB should include:

A.2.1 Title Page

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name and trade name(s) where legally permissible and desired by the sponsor) and the release date. It is also suggested that an edition number and a reference to the number and date of the edition it supersedes be provided along with the cut-off date for data inclusion in the version. Where appropriate, a signature page may be included.

A.2.2 Confidentiality Statement

The sponsor may wish to include a statement instructing the investigator and other recipients to treat the IB as a confidential document for the sole information and use of the investigator/institution, investigator site staff, regulatory authorities and the IRB/IEC.

A.3 Contents of the Investigator's Brochure

The IB should contain the following sections, each with literature references (publications or reports) included at the end of each chapter, where appropriate:

A.3.1 Table of Contents

A.3.2 Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic and clinical information available that is relevant to the stage of clinical development of the investigational product.

A.3.3 Introduction

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s); all active ingredients; the pharmacological class of the investigational product(s) and its expected position within this class (e.g., advantages); the rationale for performing research with the investigational product(s); and the anticipated prophylactic,

therapeutic or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

A.3.4 Physical, Chemical and Pharmaceutical Properties and Formulation

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

A.3.5 Nonclinical Studies

Introduction

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results and a discussion of the relevance of the findings to the investigated product and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g., milligram/kilogram (mg/kg))
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:
  - Nature and frequency of pharmacological or toxic effects
  - Severity or intensity of pharmacological or toxic effects
  - Time to onset of effects
  - Reversibility of effects
  - Duration of effects
  - Dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans and any

aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels or human equivalent dose rather than on a mg/kg basis.

(a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single toxicity
- Repeated dose toxicity
- Genotoxicity
- Carcinogenicity
- Reproductive and developmental toxicity
- Local tolerance
- Other toxicity studies

A.3.6 Effects in Humans

Introduction

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy and other pharmacological activities. Where possible, a summary of each completed clinical trial and ongoing trials where interim results are available that may inform the safety evaluation should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from clinical trials, such as from experience during marketing.

(a) Pharmacokinetics and Product Metabolism in Humans

A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

- Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution and elimination)
- Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form
- Population subgroups (e.g., sex, age and impaired organ function)
- Interactions (e.g., product-product interactions and effects of food)
- Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s))

(b) Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy and dose response that was obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions, including information on their frequency and natures for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

(c) Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, adverse drug reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

A.3.7 Summary of Data and Guidance

This section should provide an overall discussion of the nonclinical and clinical data and should summarise the information from various sources on different aspects of

the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions and of the specific tests, observations and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous clinical and nonclinical experience and on the pharmacology of the investigational product.

Appendix B. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

Clinical trials should be described in a clear, concise and operationally feasible protocol. The protocol should be designed in such a way as to minimise unnecessary complexity and to mitigate or eliminate important risks to the rights, safety, and well-being of trial participants and the reliability of data. Protocol development processes should incorporate input from relevant interested parties, where appropriate. Building adaptability into the protocol, for example, by including acceptable ranges for specific protocol provisions, can reduce the number of deviations or in some instances the requirement for a protocol amendment. Such adaptability should not adversely affect participant safety or the scientific validity of the trial. For additional information, refer to ICH E8(R1) General Considerations for Clinical Studies, ICH E9 Statistical Principles for Clinical Trials and ICH E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials.

The contents of a trial protocol should generally include the following topics, which may vary depending on the trial design. Investigator site-specific information may be provided on separate protocol page(s) or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

B.1 General Information

B.1.1 Protocol title, unique protocol identifying number and date. Any amendment(s) should also bear the amendment number(s) and date(s).

B.1.2 Name and address of the sponsor.

B.1.3 Name and title of the person(s) authorised to sign the protocol and the protocol amendment(s) for the sponsor.

B.2 Background Information

B.2.1 Name and description of the investigational product(s).

B.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

B.2.3 Summary of the known and potential risks and benefits, if any, to human participants.

B.2.4 Description of and justification for the route of administration, dosage, dosage regimen and treatment period(s).

B.2.5 A statement that the trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

B.2.6 Description of the population to be studied.

B.2.7 References to literature and data that are relevant to the trial and that provide background for the trial.

B.3 Trial Objectives and Purpose

A clear description of the scientific objectives and the purpose of the trial. Information on estimands, when defined (see ICH E9(R1)).

B.4 Trial Design

The scientific integrity of the trial and the reliability of the results from the trial substantially depend on the trial design. A description of the trial design should include:

B.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

B.4.2 A description of the type and design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design, adaptive design, platform/umbrella/basket, trials with decentralised elements) and a schematic diagram of trial design, procedures and stages.

B.4.3 A description of the measures taken to minimise/avoid bias, including:

(a) Randomisation
(b) Blinding

B.4.4 A description of the investigational product(s) and the dosage and dosage regimen of the investigational product(s), including a description of the dosage form, packaging and labelling.

B.4.5 Preparation (e.g., reconstitution) and administration instructions where applicable, unless described elsewhere.

B.4.6 A description of the schedule of events (e.g., trial visits, interventions and assessments).

B.4.7 The expected duration of the participant's involvement in the trial and a description of the sequence and duration of all trial periods, including follow-up, if any.

B.4.8 A description of the "stopping rules" or "discontinuation criteria" and "dose adjustment" or "dose interruption" for individual participants, for parts of the trial or for the entire trial.

B.4.9 Accountability procedures for the investigational product(s), including the placebo(s) and other comparator(s), if any.

B.4.10 Maintenance of treatment randomisation codes and procedures for breaking codes.

B.5 Selection of Participants

B.5.1 Participant inclusion criteria.

B.5.2 Participant exclusion criteria.

B.5.3 Mechanism for pre-screening, where appropriate, and screening of participants.

B.6 Discontinuation of Trial Intervention and Participant Withdrawal from Trial

The investigator may choose to discontinue the participant from the trial. Conversely, the participant may decide to withdraw from the trial or stop treatment with the investigational product (see Annex 1, sections 2.8.10(l), 2.8.10(m) and 2.9.1). The protocol should specify:

(a) When and how to discontinue participants from the trial/investigational product treatment;

(b) The type and timing of the data to be collected for withdrawn/discontinued participants, including the process by which the data are handled, in accordance with applicable regulatory requirements;

(c) Whether and how participants are to be replaced;

(d) The follow-up for participants who have discontinued the use of the investigational product.

B.7 Treatment and Interventions for Participants

B.7.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the criteria for dose adjustment(s), the route/mode(s) of administration and the treatment period(s), including the follow-up period(s) for participants for each investigational product treatment/trial treatment group/arm of the trial.

B.7.2 Medication(s)/treatment(s) permitted (including concomitant and rescue medication) and not permitted before and/or during the trial.

B.7.3 Strategies to monitor the participant’s adherence to treatment.

B.8 Assessment of Efficacy

B.8.1 Specification of the efficacy parameters, where applicable.

B.8.2 Methods and timing for assessing, recording and analysing efficacy parameters. Where any trial-related committees (e.g., independent data monitoring committee (IDMC)/adjudication committees) are utilised for the purpose of assessing efficacy

data, the committees' procedures, timing and activities should be described in the protocol or a separate document.

B.9 Assessment of Safety

B.9.1 Specification of safety parameters.

B.9.2 The methods, extent and timing for recording and assessing safety parameters. Where any trial-related committees (e.g., IDMC) are utilised for the purpose of assessing safety data, procedures, timing and activities should be described in the protocol or a separate document.

B.9.3 Procedures for obtaining reports of and for recording and reporting adverse events.

B.9.4 The type and duration of the follow-up of participants after adverse events and other events such as pregnancies.

B.10 Statistical Considerations

B.10.1 A description of the statistical methods to be employed, including timing and purpose of any planned interim analysis(ses) and the statistical criteria for the stopping of the trial.

B.10.2 The number of participants planned to be enrolled and the reason for the choice of sample size, including reflections on or calculations of the power of the trial and clinical justification.

B.10.3 The level of significance to be used or the threshold for success on the posterior probability in a Bayesian design.

B.10.4 The selection of participants to be included in the planned analyses, a description of the statistical methods to be employed and procedures for handling intercurrent events and accounting for missing, unused and spurious data. These should be aligned with the target estimands, when defined (see ICH E9(R1)).

B.10.5 Statement that any deviation(s) from the statistical analysis plan will be described and justified in the clinical trial report.

B.11 Direct Access to Source Records

The sponsor should ensure that it is specified in the protocol or other documented agreement that the investigator(s)/institution(s)/service provider(s) will permit trial-related monitoring, audits, regulatory inspection(s) and, in accordance with applicable regulatory requirements, review by the institutional review board/independent ethics committee (IRB/IEC), providing direct access to source records.

B.12 Quality Control and Quality Assurance

B.12.1 Description of identified critical to quality factors, associated risks and risk mitigation strategies in the trial unless documented elsewhere.

B.12.2 Summary of the monitoring approaches that are part of the quality control process for the clinical trial.

B.12.3 Description of the process for the handling of noncompliance with the protocol or GCP.

B.13 Ethics

Description of ethical considerations relating to the trial.

B.14 Data Handling and Record Keeping

B.14.1 Specification of data to be collected and the method of its collection. Where necessary, additional details should be contained in a clinical trial-related document.

B.14.2 The identification of data to be recorded directly into the data acquisition tools (i.e., no prior written or electronic record of data) and considered to be the source record.

B.14.3 A statement that records should be retained in accordance with applicable regulatory requirements.

B.15 Financing and Insurance

Financing and insurance, if not addressed in a separate agreement.

B.16 Publication Policy

Publication policy, if not addressed in a separate agreement.

Appendix C. ESSENTIAL RECORDS FOR THE CONDUCT OF A CLINICAL TRIAL

C.1 Introduction

C.1.1 Many records are generated before and during the conduct of a clinical trial. The nature and extent of those records generated and maintained are dependent on the trial design, its conduct, application of risk proportionate approaches and the importance and relevance of that record to the trial.

C.1.2 Determining which records are essential will be based on consideration of the guidance in this appendix.

C.1.3 The essential records permit and contribute to the evaluation of the conduct of a trial in relation to the compliance of the investigator and sponsor with Good Clinical Practice (GCP) and applicable regulatory requirements and the reliability of the results produced. The essential records are used as part of the investigator oversight and sponsor oversight (including monitoring) of the trial. These records are used by the sponsor's independent audit function and during inspections by regulatory authority(ies) to assess the trial conduct and the reliability of the trial results. Certain essential records may also be reviewed by the institutional review board/independent ethics committee (IRB/IEC) in accordance with applicable regulatory requirements. The investigator/institution should have access to and the ability to maintain the essential records generated by the investigator/institution before and during the conduct of the trial and retain them in accordance with applicable regulatory requirements.

C.2 Management of Essential Records

C.2.1 Records should be identifiable and version controlled (when appropriate) and should include authors, reviewers and approvers as appropriate, along with date and signature (electronic or physical), where necessary.

C.2.2 For activities that are transferred or delegated to service providers by the sponsor or investigator/institution, respectively, arrangements should be made for the access and management of the essential records throughout the trial and for their retention following completion of the trial.

C.2.3 These essential records should be maintained in or referred to from repositories held by the sponsor and by the investigator/institution for their respective records. These repositories may be referred to as a trial master file (TMF). The repository held by the investigator/institution may also be referred to as the investigator site file (ISF).

C.2.4 The sponsor and investigator/institution should maintain a record of where essential records are located, including source records. The storage system(s) used during the trial and for archiving (irrespective of the type of media used) should provide for appropriate identification, version history, search and retrieval of trial records.

C.2.5 The sponsor and investigator/institution should ensure that the essential records are collected and filed in a timely manner, which can greatly assist in the successful

management of a trial. Some essential records should generally be in place prior to the start of the trial and may be subsequently updated during the trial.

C.2.6 The sponsor and investigator/institution should retain the essential records in a way that ensures that they remain complete, readable and readily available and are directly accessible upon request by regulatory authorities, monitors and auditors. Alteration to the essential records should be traceable.

C.2.7 The sponsor and investigator/institution should ensure the retention of the essential records required to fulfil their responsibility. The original records should generally be retained by the responsible party who generated them.

C.2.8 In order to fulfil their responsibilities in the conduct of the trial, the sponsor and investigator/institution may need access to or copies of one another's relevant essential records before and during the conduct of the trial. At the end of the trial, each party should retain their essential records (see Annex 1, sections 2.12.11 and 3.16.3(a)). The record location may vary during the trial depending on the nature of the record. For example, the investigator may access relevant essential records from the sponsor (e.g., suspected unexpected serious adverse reactions (SUSAR) reports) via a sponsor-provided portal, and these essential records would need to be retained by the investigator/institution at the end of the trial.

C.2.9 When a copy is used to permanently replace the original essential record, the copy should fulfil the requirements for certified copies.

C.2.10 Some records are typically maintained and retained only by the sponsor (e.g., those related solely to sponsor activities such as data analysis) or only by the investigator/institution (e.g., those that contain confidential participant information). Some records may be retained by the sponsor and/or the investigator/institution.

C.2.11 Careful consideration should be given to the sharing of records when there are blinding considerations and when the records are subject to applicable data protection legislation. For the sharing of essential records with service providers, see section C.2.2.

C.2.12 Certain essential records may not be specific to a trial but may be related to the investigational product, facilities or processes and systems, including computerised systems, involved in running multiple trials and retained outside the trial-specific repositories (e.g., Investigator's Brochure, master services agreements, standard operating procedures, validation records).

C.3 Essentiality of Trial Records

C.3.1 The assessment of whether a record is essential and has to be retained should take into account the criteria below. Such assessment, whilst important, is not required to be documented. A structured content list for storage repository(ies) may be used to prospectively identify essential records. An essential record:

(a) Is a document that is submitted to or issued by the regulatory authority or IRB/IEC, including related correspondence and those documenting regulatory decisions or approvals/favourable opinions;

(b) Is a trial-specific procedure or plan;

(c) Is relevant correspondence or documentation of meetings related to important discussions and/or trial-related decisions that have been made related to the conduct of the trial and the processes being used;

(d) Documents the conduct of relevant trial procedures (e.g., database lock checklist produced from following data management standard operating procedures (SOPs));

(e) Documents the arrangements between parties and insurance/indemnity arrangements;

(f) Documents the compliance with the requirements and any conditions of approval from the regulatory authority or the favourable opinion of the IRB/IEC;

(g) Documents the composition and, where appropriate, the functions, correspondence and decisions of any committees involved in the trial approval or its conduct.

(h) Demonstrates that a trial-specific computerised system is validated and that non-trial-specific systems (e.g., clinical practice computerised systems) have been assessed as fit for purpose for their intended use in the trial;

(i) Is a document that has been authorised/signed by the sponsor and/or investigator to confirm review or approval;

(j) Is, where necessary, documentation that demonstrates signatures/initials of staff undertaking significant trial-related activities; for example, completing data acquisition tools;

(k) Documents what information was provided to potential trial participants and that participants' informed consent was appropriately obtained and maintained;

(l) Documents that sponsor personnel involved in the trial conduct and individuals performing significant trial-related activities on their behalf are qualified by education, training and experience to undertake their activities;

(m) Documents that the investigator and those individuals delegated significant trial-related activities by the investigator are qualified by education, training and experience to undertake their activities, particularly where the activities are not part of their normal role;

(n) Contains the data as well as relevant metadata that would be needed to allow the appropriate evaluation of the conduct of the trial;

(o) Is a document related to the sponsor or investigator oversight of trial participant safety during the trial, including compliance with safety reporting requirements between sponsors and investigators, regulatory authorities and IRBs/IECs and informing trial participants of safety information as necessary;

(p) Documents that service providers are suitably qualified for conducting their delegated or transferred activities;

(q) Documents that laboratory activities and other tests used in the trial are fit for purpose;

(r) Documents sponsor oversight of investigator site selection and monitoring and audit of the trial, where appropriate, and provides information on arising issues/noncompliance and deviations detected and implementation of corrective and preventative actions;

(s) Documents the compliance with the protocol and/or procedures for management and statistical analysis of the data and production of any interim report and the final report;

(t) Documents the collection, chain of custody, processing, analysis and retention or destruction of biological samples;

(u) Provides relevant information on the investigational product and its labelling;

(v) Provides information about the shipment, storage, packaging, dispensing, randomisation and blinding of the investigational product;

(w) Provides, where appropriate, traceability and accountability information about the investigational product from release from the manufacturer to dispensation, administration to trial participants, return and destruction or alternative disposition;

(x) Provides information on the identity and quality of the investigational product used in the trial;

(y) Documents processes and activities relating to unblinding;

(z) Documents the recruitment, pre-trial screening and consenting process of trial participants and their identity and chronological enrolment as appropriate;

(aa) Documents the existence of the trial participants and substantiates the integrity of trial data collected. Includes source records related to the trial and medical treatments and history of the trial participants;

(bb) Defines processes/practices in place in the event of a security breach in order to protect participants' rights, safety and well-being and the integrity of the data.

C.3.2 Applying the criteria in section C.3.1, the trial records that are considered essential are listed in the Essential Records Table, and these should be retained when produced.

This table is not an exhaustive list, and other trial records may also be considered essential by the sponsor or the investigator.

C.3.3 For some trial records listed in the Essential Record Table, their presence and nature are dependent on the trial design, trial conduct and risk proportionate management of the trial and may not be produced.

Essential Records Table If these trial records are produced, they are considered essential and should be retained (see sections C3.1 and C3.2). *Note: An asterisk (*) identifies those essential records that should generally be in place prior to the start of the trial (see section C2.5).*
Investigator's Brochure or basic product information brochure (e.g., summary of product characteristics, package leaflet or labelling)*
Signed protocol* and subsequent amendments during the trial
Dated, documented approval/favourable opinion of IRB/IEC of information provided to the IRB/IEC*
IRB/IEC composition*
Regulatory authority(ies) authorisation, approval and/or notification of the protocol* and of subsequent amendments during the trial (where required)
Completed signed and dated informed consent forms
Completed participant identification code list and enrolment log
- Notification by originating investigator to sponsor of serious adverse events (SAEs) and related reports, where required - Notification by sponsor and/or investigator, where required, to regulatory authority(ies) and IRB(s)/IEC(s) of suspected unexpected serious adverse reactions (SUSARs) and of other safety information - Notification by sponsor to investigators of safety information, where required
Interim or annual reports to IRB/IEC and regulatory authority(ies) (where required)
Source records
Data and relevant metadata (including documentation of data corrections) in the data acquisition tools
Final report to IRB/IEC and regulatory authority(ies), where required
Interim (where applicable) and final clinical trial reports
Sample of data acquisition tools (e.g., case report forms (CRFs), diaries, clinical outcome assessments, including patient-reported outcomes) that are provided to the investigator and/or IRB/IEC*
Sample of information given to trial participants* - Informed consent materials (including all applicable translations)

Essential Records Table If these trial records are produced, they are considered essential and should be retained (see sections C3.1 and C3.2). *Note: An asterisk (*) identifies those essential records that should generally be in place prior to the start of the trial (see section C2.5).*
- Any other documented information (e.g., instructions for use of an investigational product or a device) - Advertisement for participant recruitment
Arrangement between parties on the financial aspects of the trial*
Insurance statement*
Signed agreement between involved parties,* for example: • Investigator/institution and sponsor • Investigator/institution and service providers • Sponsor and service providers • Sponsor and IDMC and/or adjudication committee members
Documentation of selection, assessment* and oversight of service providers conducting important trial-related activities
Relevant documents evidencing qualifications of investigator(s) and sub-investigator(s) (e.g., curriculum vitae) involved in conducting the trial*
Trial-specific training records*
Documentation of delegation of trial-related activities by the investigator*
Signature sheet documenting signatures and initials, unless only electronic signatures are used (of investigator and individuals delegated by the investigator)* (can be combined with documentation of delegation above)
Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol*
Certification or accreditation or other documentation including of validation (where required) to confirm the suitability of medical/laboratory/technical procedures/tests used during the trial conduct*
Documentation of collection, processing and shipment of body fluids/tissue samples
Documentation of body fluids/tissue samples storage conditions
Record of retained body fluids/tissue samples at the end of the trial
Sample of label(s) attached to investigational product container(s)
Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or Investigator's Brochure), for example, pharmacy manual*
Shipping records for investigational product(s) and trial-related materials*
Certificate(s) of analysis of investigational product(s) shipped*
Investigational product(s) accountability at investigator site

Essential Records Table If these trial records are produced, they are considered essential and should be retained (see sections C3.1 and C3.2). *Note: An asterisk (*) identifies those essential records that should generally be in place prior to the start of the trial (see section C2.5).*
Documentation of investigational product storage conditions, including during shipment
Records of relabelling of investigational product at the investigator site
Documentation of investigational product destruction or alternative disposition
Emergency decoding procedures for blinded trials*
Master randomisation list*
Instructions for use of important trial-specific systems (e.g., interactive response technologies (IRTs) user manual, electronic CRF (eCRF) manual)*
Records demonstrating fitness for purpose (e.g., maintenance and calibration) for equipment used for important trial activities*
Treatment allocation and decoding documentation
Completed participants screening log
Site monitoring reports (including site selection,* initiation,* routine and close-out)
Centralised monitoring reports
Records and reports of noncompliance including protocol deviations and corrective and preventative actions
Documentation of relevant communications and meetings
Audit certificate
Documentation relating to data finalisation for analysis (e.g., query resolutions, SAE reconciliation, quality control reports, coding completion, output data sets)
Documentation of trial-specific computerised system validation (e.g., specifications, testing, validation report, change control)*
Documentation of the assessment of fitness for purpose for non-trial-specific computerised systems used in the trial (e.g., clinical practice computerised systems)*
Documentation relating to the statistical considerations and analysis (e.g., sample size calculations,* analysis sets decisions, analysis data sets, analysis programs, quality control records and outputs)
Trial-specific plans (e.g., risk management,* monitoring,* safety,* data management,* data validation* and statistical analysis) and procedures
Procedures,* meeting minutes and submissions to the IDMC/adjudication committee(s)

GLOSSARY

Adverse Events and Adverse Reaction-Related Definitions:

Adverse Event (AE): Any unfavourable medical occurrence in a trial participant administered the investigational product. The adverse event does not necessarily have a causal relationship with the treatment.

Adverse Drug Reaction (ADR):

- In the pre-approval clinical experience with a new investigational product or its new usages (particularly as the therapeutic dose(s) may not be established): unfavourable and unintended responses, such as a sign (e.g., laboratory results), symptom or disease related to any dose of a medicinal product where a causal relationship between a medicinal product and an adverse event is a reasonable possibility. The level of certainty about the relatedness of the adverse drug reaction to an investigational product will vary. If the ADR is suspected to be medicinal product-related with a high level of certainty, it should be included in the reference safety information (RSI) and/or the Investigator's Brochure (IB).
- For marketed medicinal products: a response to a drug that is noxious and unintended and that occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of diseases or for modification of physiological function.

(See ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.)

Serious Adverse Event (SAE): Any unfavourable medical occurrence that is considered serious at any dose if it:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

(see ICH E2A)

An important medical event that may not be immediately life-threatening or result in death or hospitalisation, that may jeopardise the participant or that may require intervention to prevent serious outcomes (see ICH E2A and E19) should generally be considered as serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR): an adverse reaction that meets three criteria: suspected, unexpected and serious.

- Suspected: There is a reasonable possibility that the drug caused the adverse drug reaction.

- Unexpected: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure or alternative documents according to applicable regulatory requirements; see **RSI**).

- Serious: See above for **SAE**.

Agreement

A document or set of documents describing the details of any arrangements on delegation or transfer, distribution and/or sharing of activities and, if appropriate, on financial matters between two or more parties. This could be in the form of a contract. The protocol may serve as the basis of an agreement.

Applicable Regulatory Requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

Assent

Affirmative agreement of a minor to participate in clinical trial. The absence of expression of agreement or disagreement should not be interpreted as assent.

Audit

A systematic and independent examination of trial-related activities and records performed by the sponsor, service provider (including contract research organisation (CRO)) or institution to determine whether the evaluated trial-related activities were conducted and the data were recorded, analysed and accurately reported according to the protocol, applicable standard operating procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

Audit Certificate

A declaration of confirmation by the auditor that an audit has taken place.

Audit Report

A record describing the conduct and outcome of the audit.

Audit Trail

Metadata records that allow the appropriate evaluation of the course of events by capturing details on actions (manual or automated) performed relating to information and data collection and, where applicable, to activities in computerised systems. The audit trail should show activities, initial entry and changes to data fields or records, by whom, when and, where applicable, why. In computerised systems, the audit trail should be secure, computer-generated and time stamped.

Blinding/Masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the participant(s) being unaware, and double-blinding usually refers to the participant(s) and investigator(s) and, if appropriate, other investigator site staff or sponsor staff being unaware of the treatment assignment(s).

Case Report Form (CRF)

A data acquisition tool designed to record protocol-required information to be reported by the investigator to the sponsor on each trial participant (see **Data Acquisition Tool**).

Certified Copy

A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information as the original, including relevant metadata, where applicable.

Clinical Trial

Any interventional investigation in human participants intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s); and/or to identify any adverse reactions to an investigational product(s); and/or to study absorption, distribution, metabolism and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.

Clinical Trial/Study Report (CSR)

A documented description of a trial of any investigational product conducted in human participants, in which the clinical and statistical description, presentations and analyses are fully integrated into a single report (see ICH E3 Structure and Content of Clinical Study Reports).

Comparator

An investigational or authorised medicinal product (i.e., active control), placebo or standard of care used as a reference in a clinical trial.

Compliance (in relation to trials)

Adherence to the trial-related requirements, GCP requirements and the applicable regulatory requirements.

Confidentiality

Prevention of disclosure to other than authorised individuals of a sponsor's proprietary information or of a participant's identity or their confidential information.

Coordinating Investigator

An investigator assigned the responsibility for the coordination of investigators at different investigator sites participating in a multicentre trial.

Computerised Systems Validation

A process of establishing and documenting that the specified requirements of a computerised system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect trial participant protection and the reliability of trial results.

Contract Research Organisation (CRO)

See **Service Provider**.

Data Acquisition Tool (DAT)

A paper or electronic tool designed to collect data and associated metadata from a data originator in a clinical trial according to the protocol and to report the data to the sponsor.

The data originator may be a human (e.g., the participant or trial staff), a machine (e.g., wearables and sensors) or a computer system from which the electronic transfer of data from one system to another has been undertaken (e.g., extraction of data from an electronic health record or laboratory system).

Examples of DATs include but are not limited to CRFs, interactive response technologies (IRTs), clinical outcome assessments (COAs), including patient-reported outcomes (PROs) and wearable devices, irrespective of the media used.

Data Integrity

Data integrity includes the degree to which data fulfil key criteria of being attributable, legible, contemporaneous, original, accurate, complete, secure and reliable such that data are fit for purpose.

Direct Access

Permission to examine, analyse and verify records that are important to the evaluation of a clinical trial and may be performed on-site or remotely. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of participants' identities and their data and sponsor's proprietary information.

Essential Records

Essential records are the documents and data (and relevant metadata), in any format, associated with a clinical trial that facilitate the ongoing management of the trial and collectively allow

the evaluation of the methods used, the factors affecting a trial and the actions taken during the trial conduct to determine the reliability of the trial results produced and the verification that the trial was conducted in accordance with GCP and applicable regulatory requirements (see Appendix C).

Good Clinical Practice (GCP)

A standard for the planning, initiating, performing, recording, oversight, evaluation, analysis and reporting of clinical trials that provides assurance that the data and reported results are reliable and that the rights, safety and well-being of trial participants are protected.

Impartial Witness

A person who is independent of the trial who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the participant or the participant's legally acceptable representative cannot read, and who reads the informed consent form and any other documented information supplied or read to the participant and/or their legally acceptable representative.

Independent Data Monitoring Committee (IDMC)

An independent data monitoring committee (e.g., data safety monitoring board) that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety and relevant efficacy data, and to recommend to the sponsor whether to continue, modify or stop a trial.

Informed Consent

A process by which a participant or their legally acceptable representative voluntarily confirms their willingness to participate in a trial after having been informed and been provided with the opportunity to discuss all aspects of the trial that are relevant to the participant's decision to participate. Varied approaches to the provision of information and the discussion about the trial can be used. This may include, for example, providing text in different formats, images and videos and using telephone or video conferencing with investigator site staff. Informed consent is documented by means of a written (paper or electronic), signed and dated informed consent form. Obtaining consent remotely may be considered when appropriate.

Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be accessed at the investigator site, at the sponsor's and/or service provider's (including CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies). Some aspects of the inspection may be conducted remotely.

Institution

Any public or private entity or agency or medical or dental organisation in whose remit clinical trials are conducted.

Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national or supranational) constituted of medical professionals and non-medical members whose responsibility is to ensure the protection of the rights, safety and well-being of human participants involved in a trial and to provide public assurance of that protection by, among other things, reviewing and approving/providing favourable opinion on the trial protocol, the suitability of the investigator(s), the facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial participants. The legal status, composition, function, operations and regulatory requirements pertaining to IRBs/IECs may differ among countries but should allow the IRB/IEC to act in agreement with GCP as described in this guideline.

Interim Clinical Trial/Study Report

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

Investigational Product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. Investigational products should be considered synonymous with drugs, medicines, medicinal products, vaccines and biological products.

Investigator

A person responsible for the conduct of the clinical trial, including the trial participants for whom that person has responsibility during the conduct of the trial. If a trial is conducted by a team of individuals, the investigator is the responsible leader of the team and may be called the principal investigator. Where an investigator/institution is referenced in this guideline, it describes expectations that may be applicable to the investigator and/or the institution in some regions. Where required by the applicable regulatory requirements, the “investigator” should be read as “investigator and/or the institution.”

Investigator’s Brochure (IB)

A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human participants (see Appendix A).

Investigator Site

The location(s) where trial-related activities are conducted and/or coordinated under the investigator’s/institution’s oversight.

Legally Acceptable Representative

An individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective participant, to the participant's participation in the clinical trial. When a legally acceptable representative provides consent on behalf of a prospective participant, activities related to the consenting process (and re-consent, if applicable) and, where relevant, activities associated with the withdrawal of consent described in this guideline are applicable to the participant's legally acceptable representative.

Metadata

The contextual information required to understand a given data element. Metadata is structured information that describes, explains or otherwise makes it easier to retrieve, use or manage data. For the purpose of this guideline, relevant metadata are those needed to allow the appropriate evaluation of the trial conduct.

Monitoring

The act of overseeing the progress of a clinical trial and of ensuring that the clinical trial is conducted, recorded and reported in accordance with the protocol, SOPs, GCP and the applicable regulatory requirement(s).

Monitoring Plan

A document that describes the strategy, methods, responsibilities and requirements for monitoring the trial.

Monitoring Report

A documented report following site and/or centralised monitoring activities.

Multicentre Trial

A clinical trial conducted according to a single protocol but at more than one investigator site.

Nonclinical Study

Biomedical studies not performed on human participants.

Protocol

A document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline, the term "protocol" refers to protocol and protocol amendments.

Protocol Amendment

A documented description of a change(s) to a protocol.

Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded) and reported in compliance with GCP and the applicable regulatory requirement(s).

Quality Control (QC)

The operational techniques and activities undertaken to verify that the requirements for quality of the trial-related activities have been fulfilled.

Randomisation

The process of deliberately including an element of chance when assigning participants to groups that receive different treatments in order to reduce bias.

Reference Safety Information (RSI)

Contains a cumulative list of ADRs that are expected for the investigational product being administered to participants in a clinical trial. The RSI is included in the Investigator's Brochure or alternative documents according to applicable regulatory requirements. Refer to ICH E2F Development Safety Update Report for more information about RSI.

Regulatory Authorities

Bodies having the power to regulate, including those that review submitted protocols and clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

Service Provider

A person or organisation (commercial, academic or other) providing a service used by either the sponsor or the investigator to fulfil trial-related activities.

Signature

A unique mark, symbol or entry executed, adopted or authorised by an individual, in accordance with applicable regulatory requirements and/or practice to show expression of will and allow authentication of the signatory (i.e., establish a high degree of certainty that a record was signed by the claimed signatory). A signature may be physical or electronic.

Source Records

Original documents or data (which includes relevant metadata) or certified copies of the original documents or data, irrespective of the media used. This may include trial participants' medical/health records/notes/charts; data provided/entered by trial participants (e.g., electronic patient-reported outcomes (ePROs)); healthcare professionals' records from pharmacies, laboratories and other facilities involved in the clinical trial; and data from automated instruments, such as wearables and sensors.

Sponsor

An individual, company, institution or organisation that takes responsibility for the initiation, management and arrangement of the financing of a clinical trial. A clinical trial may have one or several sponsors where permitted under regulatory requirements. All sponsors have the responsibilities of a sponsor set out in this guideline. In accordance with applicable regulatory requirements, sponsors may decide in a documented agreement setting out their respective responsibilities. Where the documented agreement does not specify to which sponsor a given responsibility is attributed, that responsibility lies with all sponsors.

Sponsor-Investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to or used by a participant. The term does not include any person other than an individual (e.g., the term does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

Standard Operating Procedures (SOPs)

Detailed, documented instructions to achieve uniformity of the performance of a specific activity.

Sub-Investigator

Any individual member of the clinical trial team designated and under the oversight of the investigator to perform significant trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows).

Trial Participant

An individual who participates in a clinical trial who is expected to receive the investigational product(s) or as a control. In this guideline, trial participant and participant are used interchangeably.

Trial Participant Identification Code

A unique identifier assigned to each trial participant to protect the participant's identity and used in lieu of the participant's name when the investigator reports adverse events and/or other trial-related data.

Vulnerable Participants

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental and nursing students; subordinate hospital and laboratory personnel; employees of the pharmaceutical industry; members of the armed forces; and persons kept in detention. Other vulnerable participants may include persons in nursing homes, unemployed or impoverished

persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors and those incapable of giving consent.