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

ICH HARMONISED GUIDELINE

GUIDELINE FOR GOOD CLINICAL PRACTICE

E6(R3)

Final version

Adopted on 06 January 2025

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

E6(R3)
Document History

Code	History	Date
E6	Approval by the Steering Committee under *Step 2* and release for public consultation.	27 April 1995
E6	Approval by the Steering Committee under *Step 4* and recommended for adoption to the three ICH regulatory bodies.	1 May 1996
E6(R1)	Approval by the Steering Committee of Post-*Step 4* editorial corrections.	10 June 1996
E6(R2)	Adoption by the Regulatory Members of the ICH Assembly under *Step 4*. Integrated Addendum to ICH E6(R1) document. Changes are integrated directly into the following sections of the parental Guideline: Introduction, 1.63, 1.64, 1.65, 2.10, 2.13, 4.2.5, 4.2.6, 4.9.0, 5.0, 5.0.1, 5.0.2, 5.0.3, 5.0.4, 5.0.5, 5.0.6, 5.0.7, 5.2.2, 5.5.3 (a), 5.5.3 (b), 5.5.3 (h), 5.18.3, 5.18.6 (e), 5.18.7, 5.20.1, 8.1	9 November 2016
E6(R3)	Endorsement by the Members of the ICH Assembly under *Step 2* and release for public consultation.	19 May 2023
E6(R3)	Endorsement by the Regulatory Members of the ICH Assembly under *Step 4*.	06 January 2025

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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.

Annex 1, including its Appendices, is 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 2.8.11 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 or/and 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 discontinues 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(n)).

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).

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 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 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 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 it 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.

ICH E6(R3)指南

I. 引言

药物临床试验质量管理规范(GCP)是一项涉及人类受试者的国际性伦理、科学和质量标准。按照该标准开展的临床试验将有助于确保受试者的权利、安全和福祉得到保护;确保试验的开展符合《赫尔辛基宣言》的基本原则;并确保临床试验结果的可靠性。本文件中的"试验开展"包括从规划到报告的全过程,包括规划、启动、执行、记录、监督、评估、分析和报告等相关活动。

本 ICH GCP 指南的目标是提供统一标准,以促进 ICH 成员国和地区的监管机构对临床试验数据的相互认可。

本指南基于 ICH E8(R1)《临床研究总则》中概述的关键概念。这包括培养质量文化,主动将质量设计纳入临床试验和药物开发规划,识别对试验质量至关重要的因素,适当地让利益相关方参与,并采用相称的基于风险的方法。

临床试验在规模、复杂性和成本方面差异很大。仔细评估每项试验中对质量至关重要的因素以及与这些因素相关的风险,将有助于通过关注实现试验目标的关键活动来确保效率。

指南范围

本指南适用于拟向监管部门提交的研究用产品的干预性临床试验。根据当地要求,本指南中的 GCP 原则也可适用于不用于支持上市许可申请的其他研究用产品的干预性临床试验。

附件为原则的适当解释和应用提供了基础,因此应适当考虑;但是,只要合理且能达到预期目的,可以考虑采用不同的方法来执行附件中的规定。

本指南鼓励采用基于风险和相称的方法来开展临床试验。

指南结构

本 ICH GCP 指南由原则和详细说明这些原则的附件组成,针对不同类型的临床试验提供具体细节。这些原则旨在适用于各类临床试验类型和环境,并在技术和方

法进步时保持相关性。本指南中概述的原则可以通过不同的方法来满足,应根据临床试验的预期目的进行应用。

附件 1 及其附录旨在提供如何将这些原则适当应用于临床试验的信息。可能会制定额外的附件以响应利益相关方的需求并解决试验设计和开展中的新创新。本指南应与其他与临床试验设计和开展相关的 ICH 指南一起阅读,包括多区域试验。

注 1: 就本指南而言,"研究用产品"应被视为与药物、药品、医药产品、疫苗和生物制品同义。

II. ICH GCP 原则

临床试验是支持新药开发或现有药物新用途的临床研究的基本组成部分。设计良好且执行得当的临床试验有助于回答医疗保健和药物开发中的关键问题。其结果对于循证医疗决策至关重要。设计不当和/或执行不力的试验可能会危及受试者安全,产生不充分或不可靠的结果,且不符合伦理。这会浪费资源以及研究者和受试者的努力和时间。

GCP 原则的设计具有灵活性,适用于广泛的临床试验。本指南与 ICH E8(R1)一起,鼓励深思熟虑的考虑和规划,以解决单个临床试验的具体和潜在独特方面。这包括评估试验特征,如设计要素、正在评估的研究用产品、正在处理的医疗状况、受试者特征、开展临床试验的环境以及收集的数据类型。每项临床试验都需要仔细考虑与确保试验质量相关的因素。

这些原则旨在支持试验设计和开展的高效方法。例如,数字健康技术(如可穿戴设备和传感器)可能扩展试验开展的可能方法。这些技术可以整合到现有的医疗保健基础设施中,并使临床试验中能够使用各种相关数据源。这将有助于使临床试验的开展与不断进步的科学和技术发展保持一致。在临床试验中使用技术应适应受试者特征和特定的试验设计。本指南旨在保持媒介中立,以便能够使用不同的技术。

临床试验的设计和开展可以通过获得利益相关方的观点来支持,如患者及其社区、患者倡导组织和医疗保健专业人员。他们的意见可以帮助减少不必要的复杂性,提高可行性并增加获得有意义试验结果的可能性。创新性试验设计和技术的使用可能使更广泛和更多样化的受试者人群参与进来,从而扩大试验结果的适用性。

临床试验的设计应当保护受试者的权利、安全和福祉，并确保结果的可靠性。应当实施质量源于设计的理念，以识别对确保试验质量至关重要的因素（即数据和过程），以及威胁这些因素完整性并最终影响试验结果可靠性的风险。支持试验开展的临床试验过程和风险缓解策略应当与所收集数据的重要性以及对试验受试者安全性和试验结果可靠性的风险相称。试验设计应当具有可操作性，避免不必要的复杂性。

总体原则为临床试验的开展提供了灵活的框架。这些原则贯穿临床试验的整个生命周期。这些原则适用于涉及人类受试者的试验。这些原则是相互依存的,应当整体考虑以确保试验的伦理性和结果的可靠性。

临床试验的开展应当遵循源自《赫尔辛基宣言》的伦理原则,并符合 GCP 和适用的法规要求。临床试验的设计和实施应确保受试者的权利、安全和福祉。

1.1 受试者的权利、安全和福祉是最重要的考虑因素,应优先于科学和社会的利益。

1.2 当出现可能影响受试者安全、其继续参与试验意愿或试验开展的新的安全信息时,应及时审查受试者的安全性。

1.3 应权衡可预见的风险和不便与个体受试者和社会的预期获益。只有当预期获益能够证明已知和预期风险是合理的,才能启动和继续试验。

1.4 在设计临床试验时,应仔细考虑科学目标和目的,避免不必要地排除特定受试者人群。受试者的选择过程应能代表研究用产品获批后预期受益的人群,以便结果能推广到更广泛的人群。某些试验(如早期、概念验证试验、生物等效性研究)可能不需要如此异质的人群。

1.5 应由合格的医生或在适当情况下由合格的牙医(或根据当地法规要求的其他合格医疗专业人员)对受试者的试验相关医疗护理和医疗决策承担总体责任;但是,实际的互动、医疗护理的提供和决策可由符合适用法规要求的合格医疗专业人员执行。

1.6 可识别受试者身份的信息应按照适用的隐私和数据保护要求予以保护。

知情同意是试验伦理开展的一个组成部分。临床试验的参与应当是自愿的,并基于确保受试者(或其合法代表,如适用)充分知情的同意过程。

2.1 在参与临床试验之前,应从每位受试者处获得并记录自愿给予的知情同意。对于无法提供知情同意的潜在受试者,其合法代表应以受试者的最大利益为出发点,

在参与临床试验之前提供同意。应以便于这些潜在受试者理解的方式向其告知试验信息。如果未成年人是受试者,应根据当地法规要求酌情征得该未成年人的同意(参见 ICH E11(R1)《儿科人群药品临床研究》)。

2.2 提供的过程和信息应旨在实现主要目标,即使潜在试验受试者能够评估参与试验的获益、风险和负担,并就是否参与试验做出知情决定。知情同意过程中提供的信息应清晰简明,便于潜在受试者或合法代表理解。

2.3 知情同意过程应考虑试验的相关方面,如受试者特征、试验设计、预期的医疗干预获益和风险、试验将进行的环境和背景(如紧急情况下的试验),以及可能使用技术来告知受试者(或其合法代表)并获得知情同意。

2.4 在紧急情况下,如果无法在参与试验前获得同意,应根据适用的法规要求和机构审查委员会/独立伦理委员会(IRB/IEC)批准的程序,尽快从受试者或其合法代表处获得同意。

临床试验应接受 IRB/IEC 的独立审查。

3.1 试验的开展应遵循获得 IRB/IEC 事先批准/同意的方案。

3.2 IRB/IEC 还应根据适用的法规要求对试验进行定期审查。

临床试验应当在科学上合理,符合其预期目的,并基于充分和最新的科学知识与方法。

4.1 研究用产品的现有非临床和临床信息应足以支持拟开展的临床试验。

4.2 临床试验应当科学合理,反映对研究用产品的认知和经验,包括(如适用)待治疗、诊断或预防的疾病;对基础生物学机制(疾病和研究用产品)的当前认识;以及研究用产品的目标人群。

4.3 由于试验开始后可能出现新的或未预料到的信息，应定期审查当前的科学知识和方法，以确定是否需要对试验进行修改。

临床试验应由合格人员设计和开展。

5.1 在临床试验的各个阶段可能需要具有不同专业知识和培训的人员，如医生、护士、药剂师、科学家、伦理学家、技术专家、试验协调员、监查员、稽查员和生物统计学家。参与试验的人员应通过教育、培训和经验获得执行各自任务的资格。

质量应当融入临床试验的科学和操作设计及开展中。

6.1 本指南中所述的临床试验质量被视为适合其目的。

6.2 应前瞻性地识别对试验质量至关重要的因素。这些因素是试验的属性，对于保护受试者、试验结果的可靠性和可解释性以及基于这些试验结果做出的决策都是至关重要的。质量源于设计涉及关注试验中对质量至关重要的因素，以最大限度地提高试验达到其目标的可能性。

6.3 应实施策略以避免、发现、处理并防止再次发生严重违反 GCP、试验方案和适用法规要求的情况。

临床试验过程、措施和方法的实施应与受试者风险和所收集数据的重要性相称，并避免给受试者和研究者带来不必要的负担。

7.1 试验过程应与试验固有的风险和所收集信息的重要性相称。在这种情况下的风险包括对试验受试者权利、安全和福祉的风险，以及对试验结果可靠性的风险。

7.2 重点应放在与试验参与相关的风险上。对于涉及患者的临床试验，重点应放在超出常规医疗护理相关风险的风险上。在临床试验环境中使用已获得上市许可的研究用产品的相关风险可能与患者的常规护理不同，应予以考虑。

7.3 对质量至关重要的因素的风险应主动管理，并在试验开始后出现新的或未预料到的问题时进行调整。

7.4 试验过程应具有可操作性，避免不必要的复杂性、程序和数据收集。试验过程应支持关键试验目标。申办者不应给受试者和研究者带来不必要的负担。

临床试验应在清晰、简明、科学合理且可操作的方案中描述。

8.1 设计良好的试验方案对于保护受试者和产生可靠结果至关重要。

8.2 任何试验的科学目标都应在方案中清晰明确地说明。

8.3 临床试验方案以及方案执行的计划或文件（如统计分析计划、数据管理计划、监查计划）应清晰、简明且可操作。

临床试验应产生可靠的结果。

9.1 临床试验产生的信息的质量和数量应适合其目的，并足以对试验结果提供信心并支持良好的决策。

9.2 有助于数据采集、管理和分析的系统和过程，以及有助于确保试验产生的信息质量的系统和过程，应适合其目的，应采集方案要求的数据，并应以与受试者风险和获得数据重要性相称的方式实施。

9.3 临床试验中使用的计算机系统应适合其目的（如通过基于风险的验证，如适用），并且对其质量至关重要的因素应在其设计或为临床试验目的的改编中得到解决，以确保相关试验数据的完整性。

9.4 临床试验应纳入高效和稳健的记录（包括数据）管理流程，以帮助确保维持记录完整性和可追溯性，并保护个人信息，从而允许准确报告、解释和验证相关的临床试验信息。

9.5 申办者和研究者应根据适用的法规要求，在规定期限内安全保存必要记录。这些必要记录应根据要求提供给监管机构、监查员、稽查员和 IRB/IEC（如适用），以便对试验开展进行适当评估，从而确保试验结果的可靠性。

9.6 临床试验的透明度包括及时在可公开访问和认可的数据库上注册，以及公开发布临床试验结果。应考虑向受试者传达试验结果。此类传达应客观且非推广性质。

临床试验中的角色和职责应当明确并适当记录。

10.1 申办者可以转让或研究者可以委托其任务、职责或职能（以下简称活动），但他们仍然对各自的活动承担总体责任。

10.2 协议应明确界定临床试验的角色、活动和职责，并适当记录。当活动已转让或委托给服务提供商时，试验的开展责任（包括试验数据的质量和完整性）分别仍由申办者或研究者承担。

10.3 申办者或研究者应对上述活动保持适当的监督。

临床试验中使用的研究用产品应按照适用的药品生产质量管理规范(GMP)标准生产，并按照产品规格和试验方案进行管理。

11.1 临床试验中使用的研究用产品应按照适用的 GMP 标准生产。

11.2 应采取措施确保提供给试验参与者的研究用产品保持其质量。

11.3 研究用产品应按照方案和相关试验文件使用。

11.4 研究用产品的生产、处理和标签应以符合治疗分配并保持盲法（如适用）的方式进行。

11.5 研究用产品的标签应遵循适用的法规要求。

11.6 应实施适当的流程用于研究用产品的处理、运输、储存、分发、退回和销毁或替代处置。

III. 附件 1

机构审查委员会/独立伦理委员会(IRB/IEC)

IRB/IEC 负责试验的伦理审查。本指南中关于 IRB/IEC 的要求应与当地法规要求一并阅读。

1.1 提交和沟通

对于向 IRB/IEC 提交或与其沟通，在大多数地区，如果还需要向相关监管机构提交，这些可以根据适用的法规要求合并为单一提交。根据适用的法规要求，在某些地区由研究者/机构向 IRB/IEC 和监管机构提交和沟通，而在其他地区则由申办者提交和沟通。

1.2 职责

1.2.1 IRB/IEC 的目的是保护所有试验参与者的权利、安全和福祉。应适当考虑计划招募易受伤害参与者的试验。

1.2.2 IRB/IEC 应审查以下信息（如适用）：

(a) 方案和修正案；

(b) 知情同意材料、知情同意书（如适用）及其任何更新，包括如何获得知情同意和同意的过程描述；

(c) 研究者手册或当前科学信息，如基本产品信息手册（例如，产品特性概要(SmPC)、包装说明书或标签），视情况而定，包括其更新；

(d) 将提供给试验参与者的其他试验相关信息，包括提供此类信息的媒介描述；

(e) 参与者招募广告（如使用）和招募过程信息；

(f) 补偿参与者的计划（如有）；

(g) 持续的安全性信息更新；

(h) 研究者当前的简历和/或其他证明资格的文件；

(i) IRB/IEC 为履行其职责可能需要的任何其他文件。

1.2.3 IRB/IEC 应在合理时间内审查拟议的临床试验，并记录其审查，明确标识试验、审查的文件和以下日期：

(a) 批准/同意意见；

(b) 批准/同意意见前需要进行的修改；

(c) 不批准/否定意见；

(d) 终止/暂停任何先前的批准/同意意见。

1.2.4 IRB/IEC 应根据受试者风险程度，以适当的时间间隔对每个正在进行的试验进行持续审查。

1.2.5 当 IRB/IEC 判断额外信息将有意义地增加对受试者权利、安全和/或福祉的保护时，IRB/IEC 可要求向受试者提供比第 2.8.11 节所述更多的信息。

1.2.6 当方案表明无法事先获得试验受试者或其合法代表的同意时(见第 2.8.8 节)，IRB/IEC 应确定拟议的方案和/或其他文件充分解决了相关伦理问题，并符合此类试验的适用法规要求(如在紧急情况下)。

1.2.7 如果试验将纳入未成年人，IRB/IEC 应考虑拟招募的未成年人群的年龄、成熟度和心理状态以及适用的法规要求，审查知情同意信息。

1.2.8 如果试验受试者因参与试验而获得补偿，IRB/IEC 应审查支付给受试者的金额和方式，以确保这些不会对试验受试者造成胁迫或不当影响。向受试者支付的款项应及时、按比例支付，且不应完全取决于受试者完成试验。对受试者产生的合理费用(如交通和住宿费用)的报销不构成胁迫。

1.2.9 IRB/IEC 应确保在知情同意材料和提供给受试者的任何其他信息中，列明向受试者支付的相关信息，包括支付方式、金额和时间表。

1.3 组成、职能和运作

1.3.1 IRB/IEC 应由合理数量的成员组成，这些成员共同具备审查和评估拟议试验的科学、医学方面和伦理的资格和经验。建议 IRB/IEC 应包括：

(a) 至少五名成员；

(b) 至少一名主要兴趣领域不在医学科学的成员；

(c) 至少一名独立于机构/研究者所在单位的成员。

只有那些独立于研究者和试验申办者的 IRB/IEC 成员才能投票/提供意见。应保存 IRB/IEC 成员名单及其资格证明。

1.3.2 IRB/IEC 应按照书面操作程序执行其职能，应保存其活动记录和会议记录，并应遵守 GCP 和适用的法规要求。

1.3.3 IRB/IEC 应在公布的会议上做出决定，会议应有其书面操作程序规定的法定人数出席。加急审查可采用替代程序(见第 1.4.5 节)。

1.3.4 只有参与 IRB/IEC 审查和讨论的成员才能投票/提供意见和/或建议。

1.3.5 研究者、研究者所在单位工作人员和/或申办者(如适当)可以提供有关试验任何方面的信息，但不应参与 IRB/IEC 的决策或投票/意见。

1.3.6 IRB/IEC 可以邀请在特殊领域具有专业知识的非成员提供协助。

1.4 程序

IRB/IEC 应制定、记录并遵循其程序，这些程序应包括：

1.4.1 确定其组成(成员姓名和资格)及其设立的依据；

1.4.2 安排、通知其成员并召开会议；

1.4.3 对试验进行初始和持续审查；

1.4.4 确定持续审查的适当频率；

1.4.5 根据适用的法规要求，对已获得 IRB/IEC 批准/同意意见的正在进行的试验的微小变更进行加急审查和批准/同意意见；

1.4.6 规定在 IRB/IEC 发布其书面批准/同意意见之前，不得让任何受试者参加试验；

1.4.7 规定除非为了消除对受试者的直接危害，或根据适用的法规要求，变更仅涉及试验的后勤或行政方面，否则未经 IRB/IEC 事先书面批准/同意意见，不得偏离或更改方案；

1.4.8 规定研究者/机构应及时向 IRB/IEC 报告(见第 1.1 节)：

(a) 为消除对试验受试者的直接危害而偏离方案的情况(见第 1.4.7、2.5.4 和 2.5.5 节)；

(b) 增加受试者风险和/或显著影响试验开展的变更(见第 2.4.6 节)；

(c) 根据适用的法规要求报告所有可疑的非预期严重不良反应(SUSARs)；

(d) 可能对受试者安全或试验开展产生不利影响的新信息。

1.4.9 确保 IRB/IEC(见第 1.1 节)及时以书面形式(纸质或电子)通知研究者/机构或申办者：

(a) 其与试验相关的决定/意见；

(b) 其决定/意见的理由；

(c) 对其决定/意见提出申诉的程序。

1.5 记录

1.5.1 IRB/IEC 应根据适用的法规要求保留所有相关记录(如书面程序、成员名单、成员的职业/从属关系清单、提交的文件、会议记录和通信)，并应监管机构要求时提供这些记录。

1.5.2 研究者、申办者或监管机构可要求 IRB/IEC 提供其书面程序和成员名单。

研究者

2.1 资格和培训

2.1.1 研究者应通过教育、培训和经验获得资格，以承担正确开展试验的责任，并应提供此类资格的证明。

2.1.2 研究者应熟悉方案、现行研究者手册、产品信息和/或申办者提供的其他信息来源中所述的研究用产品的适当使用方法。

2.2 资源

2.2.1 研究者应能够证明(例如，基于回顾性或当前可用数据)在与申办者商定的招募期内招募拟定数量的合格受试者的潜力。

2.2.2 研究者应有充足的时间、足够数量的合格工作人员和适当的设施，以在预期的试验期间正确和安全地开展试验。

2.3 职责

2.3.1 研究者可以将试验相关活动委托给其他人员或方。申办者可以协助研究者确定合适的服务提供商；但是，研究者根据申办者提供的信息，保留对服务提供商是否适合支持研究者的最终决定权(见第 3.6.5 节)。

研究者保留最终责任，并应对被委托活动的人员或方进行适当监督，以确保试验受试者的权利、安全和福祉以及数据的可靠性。研究者对委托活动的监督程度应取决于委托活动的性质，并与所收集数据的重要性以及对试验受试者安全和数据可靠性的风险相称。

2.3.2 研究者应确保其委托试验相关活动的人员或方具有适当的资格，并充分了解方案、研究用产品和其被分配的试验活动的相关方面(包括根据当地法规要求由其他方提供的工作人员开展的活动)。对协助试验人员的试验相关培训应与使其能够履行超出其常规培训和经验范围的委托试验活动所必需的内容相对应。

2.3.3 研究者应确保保存研究者已委托试验相关活动的人员和方的记录。委托文件应与试验相关活动的重要性相称。在活动作为临床实践的一部分执行的情况下，可能不需要委托文件。

2.3.4 研究者/机构与服务提供商就试验相关活动达成的协议应形成文件。

2.3.5 研究者/机构应允许申办者进行监查和稽查，允许相关监管机构进行检查，并根据适用的法规要求，允许 IRB/IEC 进行审查。

2.4 与 IRB/IEC 的沟通

2.4.1 根据适用的法规要求，向 IRB/IEC 提交可由研究者/机构或申办者进行(见第 1.1 节)。

2.4.2 在开始试验之前，研究者/机构应获得 IRB/IEC 对试验方案、知情同意材料、受试者招募程序(如广告)和任何其他将提供给受试者的试验相关信息的书面和注明日期的批准/同意意见。

2.4.3 作为研究者/机构或申办者(根据适用的法规要求)向 IRB/IEC 提交的一部分，应提供当前版本的研究者手册或基本产品信息手册。如果研究者手册或基本产品信息手册在试验期间更新，IRB/IEC 应根据适用的法规要求收到当前版本。

2.4.4 随着试验的进展，研究者/机构或申办者应根据适用的法规要求向 IRB/IEC 提供任何受试者信息的更新。

2.4.5 研究者或申办者应根据当地法规要求或应要求向 IRB/IEC 提交试验状态的书面总结。

2.4.6 研究者或申办者应及时向 IRB/IEC 通报显著影响试验开展和/或增加受试者风险的任何变更。

2.5 遵守方案 2.5.1 研究者/机构应签署方案或替代合同，以确认与申办者达成一致。

2.5.2 研究者应遵守方案、GCP 和适用的法规要求。

2.5.3 研究者应记录所有方案偏离。除了研究者自己发现的偏离外，申办者可能会向其通报与其试验受试者和试验开展相关的方案偏离。在任何情况下，研究者都应审查偏离情况，对于被认为重要的偏离，研究者应解释偏离原因并采取适当措施防止再次发生。

2.5.4 研究者应遵循方案，只有在需要消除对试验受试者的直接危害时才可偏离。如为消除对试验受试者的直接危害而发生偏离，研究者应及时通知申办者。

2.5.5 研究者应向 IRB/IEC 和相关监管机构报告直接危害信息、已实施的变更和随后提出的方案修正案(如有)。

2.6 提前终止或暂停试验 2.6.1 如果试验因任何原因提前终止或暂停，研究者/机构应及时通知试验受试者，并确保为受试者提供适当的治疗和随访。

2.6.2 如果研究者在未事先与申办者达成一致的情况下终止或暂停其参与试验，研究者应及时通知机构(如适用)、申办者、IRB/IEC 和监管机构，并提供详细的原因说明。

2.6.3 如果申办者终止或暂停试验，研究者/机构或申办者应根据适用的法规要求及时通知 IRB/IEC 和监管机构，并提供适当的解释。

2.6.4 如果 IRB/IEC 终止或暂停其对试验的批准/同意意见，研究者应通知机构(如适用)，研究者/机构应及时通知申办者。

2.7 受试者医疗护理和安全报告 2.7.1 试验受试者的医疗护理 (a) 作为试验研究者或分研究者的合格医生，或在适当情况下合格牙医(或根据当地法规要求的其他合格医疗专业人员)应负责试验相关的医疗护理和决策。

(b) 其他适当合格的医疗专业人员可根据其正常活动并按照当地法规要求参与试验受试者的医疗护理。

(c) 在试验期间和之后，研究者/机构应确保为受试者提供任何与试验相关的不良事件(包括临床显著的实验室值)的充分医疗护理。当研究者发现需要治疗偶发疾病时，应通知受试者。

(d) 如果受试者有主治医生且同意通知主治医生，研究者应告知主治医生其参与试验的情况。

2.7.2 安全性报告

(a) 应按照方案规定的报告要求和时限向申办者报告不良事件和/或需要进行安全性评估的异常检查结果(如方案中所述)。在研究用产品给药前发生的不良医疗事件(如筛选期间)，如果方案要求，应考虑并向申办者报告。

(b) 所有严重不良事件(SAE)应在研究者合理获知后立即向申办者报告。研究者还应包括因果关系评估。根据适用法规要求，方案可确定无需立即报告的 SAE，例如作为终点的死亡或其他事件。后续信息应根据需要作为随访报告提交。

(c) 对于报告的死亡病例，研究者应向申办者、IRB/IEC 以及监管机构(如适用)提供任何额外要求的信息(如尸检报告和临终医疗报告)。

(d) 研究者可将安全性报告活动委托给合格的研究机构工作人员，但仍需对其负责的受试者安全和遵守报告要求承担总体责任。

2.8 试验受试者的知情同意

2.8.1 在获取和记录知情同意(纸质或电子格式)时，研究者应遵守适用的法规要求，并应遵守 GCP 和源于赫尔辛基宣言的伦理原则。知情同意过程应包括：

(a) 在征得同意和招募受试者之前，研究者应获得 IRB/IEC 对知情同意材料和过程的书面批准/同意意见；

(b) 信息应尽可能清晰简洁，使用简单语言并避免不必要的冗长和复杂性。这是为了确保试验受试者或其合法代表充分理解试验目的、替代治疗、潜在获益和风险、负担、其权利以及对受试者的期望，从而能够就其参与试验做出知情决定；

(c) 在知情同意过程中可使用多种方法(如文本、图像、视频和其他互动方式)，包括向受试者提供信息。在制定知情同意材料和过程时，应考虑潜在试验人群的特征(如受试者可能不熟悉计算机系统)和获取同意方法的适用性。当使用计算机系统获取知情同意时，可为试验受试者提供使用纸质方式作为替代选择。

(d) 在适当情况下可考虑远程获取同意。

(e) 无论知情同意过程是面对面还是远程进行，研究者都应根据适用法规要求确认受试者(或其合法代表)的身份。

2.8.2 如果出现可能影响受试者继续参与试验意愿的新信息，应及时告知受试者或其合法代表。这些信息的传达和确认继续参与试验的意愿应记录在案。

应评估可能影响受试者继续参与意愿的新信息，以确定是否需要重新征得同意(如根据试验阶段，应考虑新信息是否仅与新受试者或现有受试者相关)。如果需要重新征得同意(如关于新出现的安全性问题的信息)，应在修订后的知情同意材料中明确标识新信息。修订后的知情同意材料应在使用前获得 IRB/IEC 的批准/同意意见。

2.8.3 研究者或研究机构工作人员不应强迫或不当影响受试者参与或继续参与试验。

2.8.4 在知情同意过程中向受试者或其合法代表提供的信息不应包含任何导致受试者放弃或看似放弃任何法律权利的语言，或免除或看似免除研究者、机构、申办者或其服务提供商因疏忽所应承担的责任。

2.8.5 知情同意过程应由研究者或其委托的其他研究机构工作人员根据适用法规要求进行。如果受试者无法自行提供同意(如未成年人、决策能力严重受损的患者)，受试者的合法代表应代表受试者提供同意。

2.8.6 在获得知情同意之前，研究者或其委托的研究机构工作人员应根据方案和IRB/IEC 同意意见/批准的条件，为受试者或其合法代表提供充分时间(除非有正当理由，如紧急情况)和机会询问试验细节并决定是否参与试验。应令受试者或其合法代表满意地回答有关试验的问题。

2.8.7 在参与试验之前，知情同意书应由受试者或其合法代表签名并注明日期，在适当情况下，还应由公正见证人和进行知情同意讨论的研究者或其委托的研究机构工作人员签名。研究者或其委托的研究机构工作人员通过签署同意书，证明受试者或其合法代表自愿给予同意，且同意信息已准确解释并被受试者或其合法代表理解。知情同意过程可以包括实体或电子签名和日期。

2.8.8 在紧急情况下，当无法事先获得受试者同意时，如果受试者的合法代表在场，应征求其同意。当无法事先获得受试者同意且其合法代表不在场时，受试者的入组应遵循方案和/或其他文件中描述的措施，并获得 IRB/IEC 的书面批准/同意意见，以保护受试者的权利、安全和福祉，并确保符合适用的法规要求。应尽快告知受试者或其合法代表试验情况，并适当征求同意。

2.8.9 如果受试者或其合法代表不能阅读，在整个知情同意讨论过程中应有公正见证人在场(远程或现场)。在向受试者或其合法代表宣读并解释知情同意书和任何其他信息后，如果他们口头同意参与试验，且在能够的情况下已在知情同意书上签名并注明日期，见证人应在同意书上签名并注明日期。见证人通过签署同意书，证明同意信息已准确解释并被受试者或其合法代表理解，且受试者或其合法代表自愿给予知情同意。

2.8.10 知情同意讨论和向受试者提供的知情同意材料应适当说明以下内容：

(a) 试验目的；

(b) 试验涉及研究及试验实验性方面的概述；

(c) 试验的研究用产品以及随机分配到研究用产品的概率(如适用)；

(d) 将遵循的试验程序，包括所有侵入性程序；

(e) 对受试者的期望；

(f) 受试者可合理预见的风险或不便，以及在适用情况下对受试者伴侣、胚胎、胎儿或哺乳婴儿的风险或不便；

(g) 合理预期的获益。如果受试者没有预期的临床获益，应告知受试者；

(h) 可供受试者选择的替代程序或治疗方案及其重要的潜在获益和风险；

(i) 试验相关损害时可获得的补偿和/或治疗；

(j) 受试者参与试验的任何预期按比例支付的补偿；

(k) 受试者参与试验的任何预期费用；

(l) 受试者参与试验是自愿的，可以随时决定停止使用研究用产品或退出试验，不会受到处罚或失去其应得的利益；

(m) 对停止使用研究用产品、退出试验或被终止试验的受试者的随访程序；

(n) 根据适用的法规要求，处理受试者数据的过程，包括在退出或终止参与试验时的处理；

(o) 通过同意参与试验，受试者或其合法代表允许直接查阅源文件，但须理解受试者的医疗记录的保密性将得到保护。此访问仅限于监管机构和申办者代表(如监查员或稽查员)为审查试验活动和/或审查或核实数据和记录的目的，并须符合适用的法规要求和 IRB/IEC 的要求；

(p) 识别受试者身份的记录将保密，在适用法规要求允许的范围内不会公开。如果试验结果发表，受试者的身份将保持保密。试验可能会根据适用的法规要求在可公开访问和认可的数据库中注册；

(q) 如果出现可能影响受试者继续参与试验意愿的信息，将及时告知受试者或其合法代表；

(r) 可联系获取更多试验信息和受试者权利的人员，以及在怀疑发生试验相关伤害时应联系的人员；

(s) 可能终止受试者参与试验的可预见情况和/或原因；

(t) 受试者预期的试验参与时间；

(u) 参与试验的大致受试者人数；

(v) 当申办者提供试验结果和受试者实际治疗信息时，如果受试者希望，将向其提供这些信息。

2.8.11 在参与试验之前，受试者或其合法代表应根据适用法规要求获得已签名并注明日期的知情同意书副本(纸质或电子)以及提供的任何其他知情同意材料。在试验参与期间，受试者或其合法代表应获得同意书更新版本和任何其他更新的知情同意材料副本。

2.8.12 当未成年人作为受试者时，应作为同意过程的一部分向其提供并讨论适合其年龄的知情同意信息，并适当获得未成年人参与试验的同意。根据适用法规要求，如果未成年人在试验期间达到法定同意年龄，应考虑重新征得同意的程序。

2.8.13 当临床试验包括只能在获得其合法代表同意后才能入组的受试者时，应以便于其理解的方式向受试者告知试验情况，如果受试者有能力，应适当签署并注明知情同意书或同意书的日期。

2.9 临床试验参与的结束 2.9.1 当受试者决定停止使用研究用产品或退出试验、被终止试验或达到常规试验结束时，研究者应遵循方案和/或其他方案相关文件。对于未达到常规试验结束的受试者，这可能包括避免丢失已收集数据的指示，以确保试验结果可靠，并符合适用的法规要求。一般而言，丢失已收集的数据可能导致结果偏倚，例如可能导致对研究用产品安全性特征的不准确结论。

2.9.2 尽管受试者没有义务提供提前退出试验的原因，但研究者应在充分尊重受试者权利的同时，合理努力查明原因。研究者应考虑是否适合与受试者或其合法代表进行讨论。这种讨论应关注退出原因，以确定是否有办法解决其顾虑，使受试者能够在不受不当影响的情况下重新考虑其退出决定。研究者或其委托的研究机构工作人员应考虑向受试者解释继续参与的价值，以最大限度地减少试验受试者退出。在此过程中，研究者应确保不干扰受试者随时拒绝或退出参与的决定。

2.9.3 在适当情况下，当申办者解盲后提供试验结果和所接受的治疗信息时，研究者应在适当尊重受试者知情意愿的情况下告知受试者。

2.10 研究用产品管理 2.10.1 研究用产品管理的责任，包括产品责任、处理、分发、给药和退回，由研究者/机构承担。申办者可协助研究用产品管理的某些方

面(如提供表格和技术解决方案，如计算机系统，并安排向试验受试者分发研究用产品)。

2.10.2 当研究者/机构根据当地法规要求将其部分或全部研究用产品管理活动委托给药剂师或其他人员时，受委托人员应在研究者/机构的监督下工作。

2.10.3 如果研究者已委托研究用产品管理相关活动或这些活动的某些方面已由申办者协助，研究者监督的程度将取决于多个因素，包括研究用产品的特征、给药途径和复杂性、对研究用产品安全性和上市状态的现有认知水平。

2.10.4 研究者/机构和/或药剂师或其他适当人员应保存产品交付、库存、每位受试者使用情况(包括记录向受试者提供方案规定剂量的情况)以及退回给申办者和销毁或替代处置未使用产品的记录。这些记录应包括日期、数量、批号/序列号、有效期(如适用)以及分配给研究用产品和试验受试者的唯一编码。对于已获批准的药品，可根据当地法规要求考虑替代方法。

2.10.5 研究用产品应按照申办者规定并遵照适用法规要求进行储存。

2.10.6 研究者应确保研究用产品仅按照已批准的方案使用。

2.10.7 在适用的情况下，研究者或由研究者/机构指定的人员应向每位受试者说明研究用产品的正确使用方法，并应按照适合试验的时间间隔检查每位受试者是否正确遵循使用说明。

2.10.8 研究用产品可以运送到受试者所在地，或在靠近受试者的地点（如当地药房或当地医疗中心）供应/分发。研究用产品可由研究者机构工作人员、受试者本人、照护者或医疗专业人员在受试者所在地给药。

2.10.9 研究用产品管理应按照适用的法规要求安排和进行，并应采取保障措施确保产品完整性、按方案使用产品和受试者安全。

2.11 随机化程序和揭盲 研究者应遵循试验的随机化程序（如有），对于研究者盲法试验，应确保仅按照方案要求破解治疗随机化代码。在紧急情况下，为保护受试者安全，研究者应从试验开始就做好准备，能够在不过度延迟和阻碍的情况下进行揭盲。研究者应及时记录并向申办者说明任何过早揭盲的情况（如意外揭盲、为保护试验受试者的紧急揭盲、因 SAE 导致的揭盲）。

2.12 记录 2.12.1 在生成、记录和报告试验数据时，研究者应确保其负责的数据的完整性，无论使用何种媒介。

2.12.2 研究者/机构应维护充分的源记录，包括对其负责的每位试验受试者的相关观察。源记录应可追溯、清晰可读、同期记录、原始、准确和完整。对源记录的更改应可追溯，不应掩盖原始记录，并在必要时说明原因（通过稽查追踪）。研究者应在试验开始前确定什么被视为源记录、数据采集方法及其位置，并在需要时更新此定义。应避免源记录和数据采集工具之间不必要的转录步骤。

2.12.3 研究者应由申办者及时获得数据访问权限（见第 3.16.1(k)节），并负责及时审查数据，包括来自可能影响受试者资格、治疗或安全性的外部来源的相关数据（如中心实验室数据、中心判读的影像数据、其他机构的记录，以及适当时电子患者报告结果(ePRO)数据）。方案可规定访问例外情况，例如为保护盲法。

2.12.4 研究者应确保按照方案或试验相关说明使用申办者部署的数据采集工具和其他系统。

2.12.5 研究者应确保由研究者机构完成的数据采集工具（如病例报告表(CRF)）和任何其他必需报告（如 SAE 报告）中向申办者报告的数据准确、完整、清晰可读且及时。研究者应在与申办者商定的重要时间点（如期中分析）审查并认可报告的数据（见第 3.16.1(o)节）。

2.12.6 向申办者报告的数据应与源记录一致，或解释差异。报告数据的更改或修正应可追溯，应说明原因（如必要），且不应掩盖原始记录。

2.12.7 研究者/机构应根据适用的个人数据保护法规要求，采取适当措施保护试验受试者个人信息的隐私和保密性。

2.12.8 向申办者报告的数据应使用明确的受试者代码标识，研究者/机构可通过该代码追溯到受试者身份。

2.12.9 对于研究者/机构部署的维护和保留试验数据/信息的系统，研究者/机构应确保这些数据受到保护，防止未经授权的访问、披露、传播或更改，以及不当销毁或意外丢失。

2.12.10 在临床试验中使用计算机系统时，研究者/机构应：

(a) 对于研究者/机构部署的系统，确保适当人员具有安全和可追溯的访问权限；

(b) 对于申办者部署的系统，当需要更改或撤销个人的访问权限时通知申办者；

(c) 对于研究者/机构专门为临床试验目的部署的系统，确保按照对受试者的风险和数据重要性的比例处理第 4 节中的计算机系统要求；

(d) 当研究者向试验受试者提供数据采集设备时，确保保持可追溯性并为受试者提供适当培训；

(e) 确保在研究者/机构判断可能对试验数据或系统安全性产生重大和/或持续影响的计算机系统使用和操作事件时，向申办者报告，并在适用时向 IRB/IEC 报告。

2.12.11 研究者/机构应按照附录 C 和适用法规要求的规定保存试验记录。研究者/机构应在试验开始前和进行期间控制其生成的所有必要记录。

2.12.12 研究者/机构应按照适用法规要求的规定期限或直到申办者通知研究者/机构这些记录不再需要（以较长者为准）保留必要记录。研究者/机构应采取措施确保这些记录的可用性、可访问性和可读性，并防止未经授权的访问和意外或过早销毁（见附录 C）。

2.12.13 研究者/机构应告知申办者在保留期内负责维护必要记录的人员姓名；例如，当研究者机构关闭或研究者离开机构时。

2.12.14 应监查员、稽查员、IRB/IEC 或监管机构的要求，研究者/机构应提供所有要求的试验相关记录以供直接查阅。

2.13 报告 试验完成后，研究者应在适用情况下通知机构。研究者/机构应向 IRB/IEC 提供试验结果摘要，并在适用情况下向监管机构提供任何要求的报告。

申办者

申办者的责任包括在整个临床试验生命周期中实施与风险相称的方法，以确保试验参与者的权利、安全和福祉以及试验结果的可靠性。

3.1 试验设计 3.1.1 在计划试验时，申办者应确保有足够的安全性和有效性数据（如来自非临床研究和/或临床试验和/或真实世界来源）支持在拟研究的试验人群中按特定给药途径、剂量和持续时间进行人体暴露。

3.1.2 申办者应通过识别对试验质量至关重要的因素并管理这些因素的风险，将质量纳入临床试验设计中。

3.1.3 如 ICH E8(R1)所述，申办者在制定开发计划和临床试验方案以及制定知情同意材料和任何其他面向受试者的信息时，应考虑来自广泛利益相关方的意见，例如医疗保健专业人员和患者。

3.1.4 申办者应确保试验的所有方面在操作上是可行的，并应避免不必要的复杂性、程序和数据收集。方案、数据采集工具和其他操作文件应适合目的、清晰、简明和一致。申办者不应给受试者和研究者带来不必要的负担。

3.2 资源 申办者应确保有足够的资源适当开展试验。

3.3 活动分配 在启动临床试验活动之前，申办者应确定角色并相应分配其试验相关活动。

3.4 资格和培训 申办者应在整个试验过程中使用具有适当资格的人员进行其被分配的活动（如生物统计学家、临床药理学家、医生、数据科学家/数据管理员、稽查员和监查员）。

3.4.1 医学专业知识 申办者应配备随时可用的医务人员，能够就特定试验相关的医学问题或问题提供建议。

3.5 财务 试验的财务方面应在申办者与研究者/机构之间的协议中记录。

3.6 协议 3.6.1 申办者与研究者/机构、服务提供商和参与临床试验的任何其他方（如独立数据监查委员会(IDMC)、裁定委员会）达成的协议应在启动活动前形成文件。

3.6.2 协议应在必要时更新，以反映转移活动的重大变更。

3.6.3 申办者应获得研究者/机构和服务提供商（如适用）同意：

(a) 按照已批准的方案并遵守 GCP 和适用的法规要求开展试验；

(b) 遵守数据记录/报告程序；

(c) 按照适用法规要求的规定期限或直到申办者通知研究者/机构或服务提供商（如适用）这些记录不再需要（以较长者为准）保留必要记录；

(d) 允许申办者进行监查和稽查，监管机构（国内和国外）进行检查，并按照适用法规要求允许 IRB/IEC 审查，包括允许直接查阅源记录和设施，包括服务提供商的设施。

3.6.4 申办者转让给服务提供商并由其承担的任何试验相关活动都应在协议中记录。未明确转让给服务提供商并由其承担的申办者试验相关活动仍由申办者保留。

3.6.5 申办者应向研究者提供有关申办者指定的承担研究者职责下任何活动的服务提供商的信息。此类活动的责任仍由研究者承担（见第 2.3.1 节）。

3.6.6 申办者可根据适用法规要求将任何或所有申办者试验相关活动转让给服务提供商；但是，申办者试验相关活动的最终责任，包括保护受试者权利、安全和福祉以及试验数据可靠性，仍由申办者承担。用于执行临床试验活动的任何服务提供商都应实施适当的质量管理，并向申办者报告可能影响试验受试者安全和/或试验结果的事件。

3.6.7 申办者负责评估服务提供商的适用性并进行选择，以确保他们能够充分承担转让给他们的活动。申办者应在必要时向服务提供商提供方案以及他们执行活动所需的任何其他文件。

3.6.8 申办者应能够获取相关信息（如标准操作规程和绩效指标）以选择和监督服务提供商。

3.6.9 申办者应确保对转让给服务提供商的重要试验相关活动进行适当监督，包括服务提供商进一步分包的活动。

3.6.10 服务提供商执行的试验相关活动应按照相关 GCP 要求进行，这些要求可以通过服务提供商现有的质量管理流程来满足，这些流程虽然不是专门设计用于符合 GCP，但在试验背景下适合其目的。

3.6.11 根据适用法规要求，临床试验可以有一个或多个申办者。对于有多个申办者的试验，申办者之间应有一份记录在案的协议，根据当地法规要求和/或实践规定其各自的责任。如果记录在案的协议未指明某项责任归属于哪个申办者，则该责任由所有申办者承担。

3.7 研究者选择 3.7.1 申办者负责选择研究者/机构。每位研究者应具备适当的教育、培训和经验资质，并应证明其有足够的资源和设施来正确开展试验。如果在多中心试验中使用协调委员会和/或协调研究者，其组织和/或选择是申办者的责任，其角色和责任应在其参与试验之前记录在案。

3.7.2 申办者应向潜在研究者/机构提供方案和最新的研究者手册，并给予充分时间审查方案和所提供的信息。

3.8 与 IRB/IEC 和监管机构的沟通 3.8.1 向监管机构通知/提交 根据适用法规要求，在启动临床试验之前，申办者（或申办者和研究者）应向适当的监管机构提交任何所需的申请，以供审查、接受和/或获准开始试验。任何通知/提交都应注明日期，并包含足够的信息以识别方案。

3.8.2 确认 IRB/IEC 的审查 (a) 如果提到向 IRB/IEC 提交，这可以由研究者/机构或申办者根据适用法规要求进行（见第 1.1 节）。(b) 申办者应确保获得以下内容：(i) 相关 IRB/IEC 的名称和地址，以及：(aa) 一份声明，说明其按照 GCP 和适用法规要求组织和运作；(bb) 记录在案的初始和后续 IRB/IEC 批准/同意意见以及任何试验终止或批准/同意意见的暂停。

3.9 申办者监督 3.9.1 申办者应确保试验设计和试验实施、所进行的过程以及生成的信息和数据具有足够的质量，以确保试验结果可靠、试验受试者安全和适当的决策。

3.9.2 申办者应确保试验过程按照试验方案和相关文件以及适用的法规要求和伦理标准进行。

3.9.3 申办者应确定必要的试验特定标准，用于将方案偏差分类为重要偏差。重要方案偏差是方案偏差的一个子集，可能会显著影响试验数据的完整性、准确性和/或可靠性，或可能显著影响受试者的权利、安全或福祉。

3.9.4 与试验相关的决策应适当评估其对受试者权利、安全和福祉以及试验结果可靠性的影响。在试验的计划、实施和报告过程中，应适当管理与此类决策相关的风险。

3.9.5 监督措施的范围和程度应适合目的，并根据试验的复杂性和相关风险进行调整。研究者和服务提供商的选择和监督是监督过程的基本特征。申办者的监督包括与研究者和服务提供商的试验相关活动有关的质量保证和质量控制过程。

3.9.6 申办者应确保适当和及时地上报和跟进问题，以便及时实施适当的行动。

3.9.7 申办者可考虑设立独立数据监查委员会(IDMC)，定期评估临床试验的进展，包括安全性数据和有效性终点，并向申办者建议是否继续、修改或停止试验。

3.9.8 在适当情况下，申办者还可在某些试验中设立终点评估/裁定委员会，审查研究者报告的终点，以确定终点是否符合方案规定的标准。为最大限度地减少偏倚，无论试验本身是否采用盲法进行，此类委员会在进行评估时通常应对分配的治疗保持盲态。

3.9.9 为可能影响受试者安全或试验结果可靠性的目的而设立的委员会应包括具有相关专业知识且利益冲突得到管理的成员，应有书面操作规程（如章程），并记录其决定。

3.10 质量管理 申办者应在试验过程的所有阶段实施适当的质量管理系统。质量管理包括设计和实施高效的临床试验方案，包括试验实施的工具和程序（包括数据收集和管理），以确保受试者权利、安全和福祉的保护以及试验结果的可靠性。申办者应采用与质量管理相称的风险基础方法，这涉及将质量纳入临床试验设计（即设计质量）并识别那些可能对受试者权利、安全和福祉以及结果可靠性产生有意义影响的因素（即 ICH E8(R1)中描述的关键质量因素）。申办者应在临床试验报告中描述试验中实施的质量管理方法（见 ICH E3 临床研究报告的结构和内容）。

3.10.1 风险管理 下面描述了识别和管理风险的相称方法：

3.10.1.1 风险识别 申办者应在试验启动前和整个试验实施过程中识别可能对关键质量因素产生有意义影响的风险。应考虑临床试验中使用的过程和系统（包括计算机系统）的风险（如试验设计、受试者选择、知情同意过程、随机化、盲法、研究用产品给药、数据处理和服务提供商活动）。

3.10.1.2 风险评估 申办者应通过考虑以下方面评估已识别的风险和现有的控制措施：(a) 伤害/危害发生的可能性；(b) 此类伤害/危害的可检测程度；(c) 此类伤害/危害对试验受试者保护和试验结果可靠性的影响。

3.10.1.3 风险控制 风险控制应与风险对受试者权利、安全和福祉以及试验结果可靠性的重要性相称。风险缓解活动可以纳入方案设计和实施、监查计划、界定各方角色和责任的协议以及培训中。

在相关情况下，申办者应设定预先规定的可接受范围（如试验层面的质量容限），以支持对关键质量因素风险的控制。这些预先规定的范围反映了超出时可能影响受试者安全或试验结果可靠性的限度。当检测到超出这些范围的偏差时，应进行评估以确定是否存在可能的系统性问题以及是否需要采取行动。

3.10.1.4 风险沟通 申办者应记录并沟通已识别的风险和缓解活动（如适用）给那些参与采取行动或受此类活动影响的人员。沟通还有助于在临床试验实施期间进行风险审查和持续改进。

3.10.1.5 风险审查

申办者应定期审查风险控制措施，考虑新出现的知识和经验，确定已实施的质量管理活动是否仍然有效和相关。必要时可实施额外的风险控制措施。

3.10.1.6 风险报告

申办者应总结并报告重要质量问题（包括超出可接受范围的情况，如第 3.10.1.3 节所述）和采取的补救措施，并在临床试验报告中记录（见 ICH E3）。

3.11 质量保证和质量控制

申办者负责建立、实施和维护适当的质量保证和质量控制流程以及文件化程序，以确保试验的开展和数据的生成、记录和报告符合方案、GCP 和适用的法规要求。

3.11.1 质量保证

质量保证应贯穿整个临床试验，包括实施基于风险的策略，以识别可能或实际导致严重违反方案、GCP 和/或适用法规要求的原因，从而采取纠正和预防措施。

3.11.2 稽查

当进行稽查时，应以与试验开展相关的风险相称的方式进行（见第 3.10.1.1 节）。申办者稽查的目的是独立于且区别于常规监查或质量控制职能，旨在评估为管理和开展试验而建立的流程是否适当，以确保符合方案、GCP 和适用的法规要求。

3.11.2.1 稽查员的选择和资格

(a) 申办者应任命独立于被稽查的临床试验/流程的人员。

(b) 申办者应确保稽查员经过培训并具有经验，能够正确进行稽查。

3.11.2.2 稽查程序

(a) 申办者应确保按照申办者的文件化程序进行临床试验/流程的稽查，包括稽查内容、方式（即现场和/或远程）、频率以及稽查报告的形式和内容。

(b) 申办者的试验稽查计划、方案和程序应考虑诸如试验对监管机构提交的重要性、试验参与者数量、试验类型和复杂性、试验参与者的风险水平以及任何已识别的问题等因素。

(c) 稽查员的观察和发现应予以记录。

(d) 为保持稽查职能的独立性和价值，监管机构不应常规要求稽查报告。监管机构可在具体情况下寻求获取稽查报告（即当存在严重违反 GCP 的证据或怀疑，或在法律程序过程中）。

(e) 当适用法规要求时，申办者应提供稽查证书。

3.11.3 质量控制

质量控制应采用基于风险的方法应用于数据处理的每个阶段，以确保数据可靠且已正确处理。在临床试验中，监查和数据管理流程是主要的质量控制活动。在适当情况下，质量控制活动也可应用于研究者机构以外的设施（如中心影像读取设施）。

3.11.4 监查

监查的目的是在试验进行过程中确保参与者的权利、安全和福祉以及试验结果的可靠性。监查是主要的质量控制活动之一。

监查涉及广泛的活动，包括但不限于与研究者机构的沟通、验证研究者和研究者机构工作人员的资格和机构资源、培训和审查试验文件和信息，使用各种方法包括源数据审查、源数据验证、数据分析以及访问开展试验相关活动的机构设施。某些监查活动（如集中监查）可由具有不同角色的不同人员（如数据科学家）使用不同方法进行。但是，监查应由未参与被监查机构临床试验实施的人员执行。监查方法应考虑所涉及的活动和服务，包括分散式环境，并应包含在监查计划中。监查员和其他试验工作人员应遵守数据保护和保密要求，符合适用的法规要求、机构政策和既定的数据安全标准。

根据监查策略和临床试验设计的不同，监查可能包括现场监查（现场和/或远程进行）和集中监查。

申办者应根据已识别的风险确定适当的监查范围和性质。应考虑诸如目标、目的、设计、复杂性、盲法、试验参与者数量、研究用产品、当前安全性特征认知和试验终点等因素。

3.11.4.1 研究者机构监查

(a) 可以对研究者机构（包括其药房和当地实验室，如适用）的临床试验活动进行监查。监查活动的频率也应根据已识别的风险确定。应根据获得的知识适当修改监查活动及其频率。

(b) 根据活动性质及其目标，此监查活动可以现场和/或远程进行。

(c) 监查可包括对源记录、其他数据采集工具和必要记录保存系统的远程和安全的只读访问。

3.11.4.2 集中监查

(a) 集中监查是由申办者的合格和经过培训的人员（如医学监查员、数据科学家/数据管理员、生物统计学家）及时对累积数据进行的评估。

(b) 集中监查过程提供额外的监查能力，可以补充并减少现场监查的范围和/或频率，或单独使用。使用集中数据分析可以帮助识别系统性或特定机构的问题，包括方案不依从和潜在的不可靠数据。

(c) 集中监查可支持选择机构和/或过程进行有针对性的现场监查。

3.11.4.3 监查计划

申办者应制定针对已识别的潜在安全风险、数据质量风险和/或其他影响试验结果可靠性风险的监查计划。应特别注意与参与者安全和试验终点相关的程序。该计划应描述监查策略、所有相关方的监查活动、将使用的各种监查方法和工具，以及使用这些方法和工具的理由。监查策略应确保对试验实施的适当监督，并考虑机构能力和潜在负担。该计划应关注对质量至关重要的方面。监查计划应参考申办者的适用政策和程序。

对研究者机构外进行的重要数据和过程（如与主要终点和关键次要终点相关的数据和过程，以及旨在确保参与者安全的过程）的监查（如中心影像读取设施、中央实验室）应在监查计划中说明。

3.11.4.4 监查程序

执行监查的人员应遵循申办者的监查计划和适用的监查程序。

3.11.4.5 监查活动

按照申办者要求和监查计划进行的监查通常应包括整个临床试验生命周期中的以下活动（如适用）。

3.11.4.5.1 与开展试验各方的沟通

(a) 在申办者与研究者及其他参与试验实施的各方和个人（如集中进行的活动）之间建立和维持沟通渠道。通常，每个机构应有一名指定的监查员作为联系点。

(b) 将相关的方案、GCP 和适用法规要求的偏差告知研究者或其他参与试验实施的各方和个人，并在必要时采取适当行动防止检测到的偏差再次发生。应突出重要偏差，并应适当关注补救措施。

(c) 将源记录和/或数据采集工具中的录入错误或遗漏告知研究者或其他参与试验实施的各方和个人，并确保适当进行更正、补充或删除，注明日期并说明（如有必要），并适当记录对更改的批准。

(d) 针对偏差、错误或遗漏采取的行动应与其重要性相称。

3.11.4.5.2 研究者机构选择、启动、管理和结束

(a) 选择机构并确认研究者和参与试验实施的个人或各方具有足够的资质、资源（见第 2.1、2.2 和 3.7 节）和设施，包括实验室、设备和研究者机构工作人员，以安全和适当地开展试验。

(b) 考虑其委托的活动和经验，确认研究者、研究者机构工作人员和其他各方以及参与试验实施的个人充分了解试验情况，并遵循当前已批准的方案和其他方案相关文件，如现行的研究者手册以及与研究用产品相关的相关信息。

(c) 确认研究者保持必要记录（见附录 C）。

(d) 确认在试验参与者参与试验前已获得知情同意（见第 2.8 节）。

(e) 确定不良事件是否在方案、GCP 和适用法规要求规定的时限内得到适当报告。

(f) 确认方案对源记录的要求和机构此类数据的位置。

(g) 验证盲法在适用情况下得到维持。

(h) 审查并报告参与者招募和保留率。

(i) 确认研究者按照方案和试验程序提供所需的报告、通知或其他信息。

(j) 在机构结束活动期间，确认对必要记录的保留安排以及研究用产品的最终核算（如退回和销毁或适当的替代处置）。

3.11.4.5.3 研究用产品管理的监查

(a) 对研究用产品确认：

(i) 储存条件可接受且符合方案或其他相关文件规定的储存要求；

(ii) 供应在整个试验期间充足且在有效期内使用；

(iii) 仅向符合条件的参与者按方案规定的剂量提供正确的研究用产品，并在适当情况下按照随机化程序进行；

(iv) 向参与者、研究者、研究者机构工作人员和其他相关各方及参与试验实施的个人提供关于正确储存、使用、处理、退回和销毁或研究用产品替代处置的必要指导；

(v) 研究用产品的接收、储存、使用、处理、退回和销毁或替代处置得到充分控制和记录；

(vi) 未使用的研究用产品的处置符合适用的法规要求并符合申办者要求；

(vii) 如果使用市场上可获得的产品并按照适用的法规要求分发和使用，前述某些考虑可能不适用。

3.11.4.5.4 临床试验数据的监查

(a) 验证研究者仅招募符合条件的试验参与者。

(b) 检查报告的试验数据与源记录和其他试验相关记录的准确性、完整性和一致性，以及这些是否及时报告。这可以基于使用样本并在适当情况下由数据分析支持来完成。样本量和数据或记录类型可能需要根据以前的监查结果或其他数据质量不足的迹象进行调整。监查应：

(i) 验证方案要求的数据和监查计划中确定为较高重要性的数据与源一致；

(ii) 识别缺失数据、不一致数据、数据异常值、意外的变异性缺乏和方案偏差；

(iii) 检查数据趋势，如机构内部和机构之间数据的范围、一致性和变异性；

(c) 识别机构内或跨机构的重大数据采集和报告错误、潜在的数据操纵和数据完整性问题。

3.11.4.6 监查报告

(a) 监查活动报告应包括所审查内容的摘要、重要发现的描述、结论和解决所需的行动，以及对其解决情况的跟进，包括以前报告中未解决的问题。监查报告的要求（包括其内容和频率）应在申办者的程序中说明。

(b) 研究者机构和/或集中监查的报告应按照申办者程序的规定及时提供给适当的申办者工作人员进行审查和跟进。

(c) 必要时，报告应描述需要上报以采取行动和解决的发现。申办者应决定采取适当的行动，并在必要时记录这些决定和相关行动的解决情况。

3.12 不依从

3.12.1 当研究者/机构或申办者工作人员不遵守方案、标准操作规程、GCP 和/或适用的法规要求时，申办者应采取适当和相称的行动以确保依从。

3.12.2 如果发现显著影响或可能显著影响试验参与者权利、安全或福祉或试验结果可靠性的不依从情况，申办者应进行根本原因分析，实施适当的纠正和预防措

施，并确认其充分性，除非有其他合理理由。当申办者发现可能显著影响试验参与者权利、安全或福祉或试验结果可靠性的问题（即严重不依从）时，申办者应根据适用的法规要求通知监管机构和/或 IRB/IEC，和/或研究者（如适当）。

3.12.3 如果发现研究者/机构或服务提供商存在严重不依从情况，且尽管采取补救措施仍持续存在，申办者应考虑终止研究者/机构或服务提供商参与试验。在这种情况下，申办者应及时通知监管机构和 IRB/IEC 严重不依从情况（如适当），并采取措施将对试验参与者和结果可靠性的影响降至最低。

3.13 安全性评估和报告

申办者负责对研究用产品进行持续的安全性评估。研究者手册或适用情况下的当前科学信息（如基本产品信息手册）构成临床试验安全性评估和报告的基础。更多信息见附录 A。

3.13.1 申办者对安全性信息的审查

申办者应适当汇总并及时审查相关安全性信息。这包括审查在研究用产品给药前（如筛选期间）参与者发生的任何不良医疗事件报告。这可能导致需要更新方案、研究者手册、知情同意材料和相关文件。

申办者应审查可获得的新出现的安全性信息，评估是否有任何新数据可能影响参与者继续参与试验的意愿、影响试验的开展，或改变 IRB/IEC 和/或监管机构的批准/同意意见（如适用）。任何此类信息都应及时传达给参与者、研究者、IRB/IEC 和监管机构（如适用）。

申办者应考虑是否需要因紧急危害而修改方案。如果需要，研究者/机构或申办者应向 IRB/IEC 和/或监管机构提交关于紧急危害的信息以及任何后续的方案修订（根据适用的法规要求）。

3.14 对参与者和研究者的保险/赔偿/补偿

3.14.1 如果适用法规要求，申办者应提供保险或对研究者/机构因试验引起的索赔提供赔偿（法律和财务保障），但因渎职和/或疏忽引起的索赔除外。

3.14.2 申办者的政策和程序应根据适用的法规要求，说明试验相关伤害情况下试验参与者治疗费用的处理方式。

3.14.3 对试验参与者的补偿方式应符合适用的法规要求。

3.15 研究用产品

3.15.1 研究用产品信息

申办者应确保制定研究者手册，并在获得研究用产品的重要新信息时进行更新。或者，对于已获批准的药品，申办者应确定试验中使用的基本产品信息（见附录A，A.1.1 节）。

3.15.2 研究用产品的生产、包装、标签和编码

(a) 申办者应确保研究用产品（包括活性对照和安慰剂，如适用）根据产品开发阶段进行适当表征，按照适用的 GMP 生产，并以保护盲法的方式进行编码和标签（如适用）。此外，标签应符合适用的法规要求。

(b) 申办者应确定研究用产品可接受的储存温度、储存条件（如避光）和有效期，适当的复溶液和程序，以及产品给药装置（如有）。申办者应将这些确定的内容告知所有相关方（如监查员、研究者、药剂师、储存管理人员）。

(c) 研究用产品的包装应能防止在运输和储存过程中发生污染和不可接受的变质。

(d) 在盲法试验中，申办者应实施：

(i) 对个人（包括申办者工作人员、试验参与者、研究者和/或研究者机构工作人员，视情况而定）实施研究用产品身份和分配的盲法过程，以及防止和检测不当揭盲的过程；

(ii) 在医疗紧急情况下需要揭盲时，允许研究者快速识别产品的程序和机制，同时保护其他试验参与者的治疗分配身份；

(iii) 在为向监管机构和/或 IRB/IEC 进行安全性报告而需要揭示参与者治疗分配时，保护试验盲法的机制（如适当）。

(e) 如果在临床开发过程中对研究用产品（包括活性对照和安慰剂，如适用）进行重大配方改变，在临床试验中使用新配方之前，应获得对制剂产品进行的任何额外研究结果（如稳定性、溶出率、生物利用度），以评估这些改变是否会显著改变产品的药代动力学特征。

3.15.3 研究用产品的供应和处理

(a) 申办者负责向研究者/机构供应研究用产品。在适当情况下，申办者可根据适用的法规要求向试验参与者供应研究用产品。研究用产品应在获得 IRB/IEC 和监管机构对试验的必要批准/同意意见后供应。可以采取各种运输和分发方式，例

如考虑研究用产品的特性、给药途径和复杂性以及对研究用产品安全性特征的现有认知水平。研究用产品管理应按照适用的法规要求安排和进行，并应采取保障措施确保产品完整性、按方案使用产品和参与者安全。

(b) 申办者应确保向研究者/机构或试验参与者提供关于研究用产品处理和储存的说明。程序应考虑充分和安全的接收、处理、储存、分发、从参与者处回收未使用产品以及向申办者返还未使用的研究用产品（或经申办者授权并符合适用法规要求的替代处置方式）。

(c) 申办者应：

(i) 根据适用法规要求，及时向研究者或试验参与者（如适当）提供研究用产品，以避免试验中断并确保参与者能继续治疗；

(ii) 保存记录，记录研究用产品的标识、运输、接收、退回和销毁或替代处置（见附录 C）；

(iii) 维持一个流程用于回收研究用产品并记录此类回收（如因产品缺陷召回、试验完成后退回和销毁或替代处置，或过期产品回收）；

(iv) 维持一个流程用于处置未使用的研究用产品并记录此类处置；

(v) 采取措施确保研究用产品在使用期间保持稳定，且仅在当前有效期内使用；

(vi) 保留足够数量的试验中使用的研究用产品，以便在必要时重新确认规格，并保存批次样品分析和特性记录。样品应保存至试验数据分析完成或按适用法规要求保存，以较长者为准。在使用未经修改的已获批准药品作为研究用产品的试验中，根据当地法规要求，申办者可能不需要保存样品。在这种情况下，样品通常由制造商保存。

3.16 数据和记录

3.16.1 数据处理

(a) 申办者应确保所生成和管理的数据的完整性和保密性。

(b) 申办者应对数据处理的相关阶段应用质量控制，以确保数据质量足以产生可靠的结果。申办者应将其质量保证和质量控制活动（包括数据审查）集中在较高重要性的数据和相关元数据上。

(c) 申办者应在方案中预先规定要收集的数据及其收集方法（见附录 B）。必要时，其他细节（包括数据流程图）应包含在方案相关文件中（如数据管理计划）。

(d) 申办者应确保数据采集工具适合其目的并设计用于采集方案要求的信息。这些工具应在试验中需要使用前经过验证并准备就绪。

(e) 申办者应确保实施文件化流程，以确保整个数据生命周期的数据完整性（见第 4.2 节）。

(f) 申办者应实施措施确保盲法的保护（如在数据录入和处理过程中维持盲法）。

(g) 申办者应制定程序描述揭盲（如适用）；这些描述应包括：

(i) 谁在什么时间点因何目的被揭盲；

(ii) 谁应保持盲态；

(iii) 用于维持盲法的保障措施。

(h) 申办者应向研究者/机构、服务提供商和试验参与者（如相关）提供关于数据采集、数据更改、数据保留和数据处置期望的指导。

(i) 除非有正当理由，并事先得到研究者同意且有记录，否则申办者不应更改研究者或试验参与者输入的数据。

(j) 申办者应允许在研究者/参与者要求时对数据（包括参与者输入的数据）进行错误更正。此类数据更正应有正当理由，并在原始录入时间附近有源记录支持。

(k) 申办者应确保研究者在试验过程中能及时访问根据方案收集的数据，包括来自外部来源的相关数据（如中心实验室数据、集中读取的影像数据，以及适当情况下的电子 PRO 数据）。这使研究者能够做出决定（如关于资格、治疗、继续参与试验和个别试验参与者的安全护理）（见第 2.12.3 节）。申办者不应共享可能导致研究者揭盲的数据，并应在方案中包含适当规定。

(l) 申办者不应对数据采集工具中采集的数据拥有独占控制权，以防止无法检测的更改。

(m) 申办者应确保研究者能够访问为保留目的所需的数据。

(n) 申办者应确保研究者收到关于如何浏览系统、数据和其负责的试验参与者相关元数据的指导。

(o) 申办者应在预定的重要时间点寻求研究者对其报告数据的确认。

(p) 申办者应确定在分析前需要进行的数据管理步骤，以确保数据质量充分。这些步骤可能因要进行的分析目的而异（如用于 IDMC、中期分析或最终分析的数据）（见第 4.2.6 节）。这些步骤的完成应有记录。

(q) 对于计划的中期分析，应根据达到足够分析质量的步骤来管理数据的访问和更改能力。

(r) 在提供最终分析数据之前，以及在适用情况下在试验揭盲之前，应限制对数据采集工具的编辑访问。

(s) 申办者应使用明确的试验参与者识别代码，允许识别每个参与者的所有报告数据。

(t) 申办者应根据适用的个人数据保护法规要求，采取适当措施保护试验参与者个人信息的隐私和保密性。

(u) 根据适用的法规要求并与方案一致，申办者应描述当参与者退出或中止试验时如何处理参与者数据的流程。

(v) 申办者应确保试验数据受到保护，防止未经授权的访问、披露、传播或更改，以及不当销毁或意外丢失。

(w) 申办者应建立流程和程序，向相关方（包括监管机构）报告对试验数据有重大影响的事件（包括安全漏洞）。

(x) 在临床试验中使用计算机化系统时，申办者应：

对于申办者部署的系统：

(i) 保存临床试验中使用的重要计算机化系统的记录。这应包括每个计算机化系统的用途、功能、接口和验证状态，以及负责其管理的人员。记录还应包括已实施的访问控制以及内部和外部安全措施的描述；

(ii) 确保计算机化系统的要求（如验证、稽查跟踪、用户管理、备份、灾难恢复和 IT 安全的要求）得到解决和实施，并有文件化程序和充分的培训，以确保临床试验中计算机化系统的正确开发、维护和使用（见第 4 节）。这些要求应与计算机化系统的重要性及其预期处理的数据或活动相称；

(iii) 维护授权访问系统的个人用户、其角色和访问权限的记录；

(iv) 确保授予研究者机构工作人员的访问权限符合研究者的委托，并对研究者可见；

(v) 确保有流程让服务提供商和研究者向申办者报告发现的系统缺陷；

对于研究者/机构使用或部署的系统：

(vi) 评估这些系统（如被确定为试验中包含源记录的系统，如电子健康记录、其他源数据采集记录保存系统和研究者机构文件）是否适合其目的，或已知问题的风险是否可以适当缓解。这种评估应在选择临床试验机构过程中进行，并应有记录；

(vii) 在考虑在临床试验中使用临床实践计算机化系统的情况下（如研究者/机构使用或部署的电子健康记录或影像系统），应评估这些系统在试验背景下是否适合其目的；

(viii) 评估应在试验中使用前进行，并应与系统管理的数据重要性相称。应适当考虑数据安全（包括备份措施）、用户管理和稽查跟踪等因素，这些因素有助于确保试验数据的保密性和完整性；

对于所有系统：

(ix) 确保建立流程，使服务提供商和研究者/机构能够按照第 3.12 节的规定，向申办者报告可能构成严重不依从的事件，这些事件包括对临床试验方案、试验程序、适用法规要求或 GCP 的不依从。

3.16.2 统计编程和数据分析

本节关于临床试验统计活动操作方面的文档应与 ICH E9《临床试验统计原则》和 ICH E9(R1)《临床试验统计原则指南的估计量和敏感性分析附录》一起阅读，后者为临床开发、试验设计、实施、分析和报告的统计原则提供了详细指导。

(a) 申办者应制定与试验方案一致的统计分析计划，详细说明数据分析方法，除非方案中已充分描述数据分析方法。

(b) 申办者应确保实施适当且有记录的统计编程和数据分析质量控制（如样本量计算、IDMC 审查的分析结果、临床试验报告的输出、统计或集中监查）。

(c) 申办者应确保数据处理和分析过程中数据转换和推导的可追溯性。

(d) 申办者应确保预先定义将试验参与者纳入或排除任何分析集的标准（如在方案或统计分析计划中）。对任何参与者（或特定数据点）的排除理由应清楚描述并记录。

(e) 偏离计划的统计分析或在试验揭盲后（如适用）对数据进行的更改应清楚记录并证明合理性，且仅应在特殊情况下发生（如必须解决影响试验结果可靠性的

数据差异）。此类数据更改应得到研究者授权并在稽查跟踪中反映。揭盲后的数据更改和偏离计划的统计分析应在临床试验报告中报告。

(f) 申办者应保留与试验结果报告中包含或使用的输出相关的统计编程记录，包括所执行的质量控制/验证活动。输出应可追溯到统计软件程序，带有日期和时间戳，防止任何更改，并实施访问控制以避免不当查看可能引入偏倚的信息。

3.16.3 记录保存和保留

(a) 申办者（或后续数据所有者）应按照适用法规要求保留与试验相关的申办者特定的必要记录（见附录 C）。

(b) 申办者应以书面形式告知研究者/机构和服务提供商（如适当）必要记录的保留要求，并在试验相关记录按照适用法规要求不再需要时以书面形式通知研究者/机构和服务提供商（如适当）。

(c) 申办者应按照适用法规要求向相关主管部门报告必要记录所有权的任何转让。如果试验申办方发生变更，申办者也应通知研究者。

3.16.4 记录访问

(a) 申办者应确保在方案或其他文件协议中规定，研究者/机构提供源记录的直接访问权限，用于试验相关监查、稽查、监管检查，以及按照适用法规要求进行的 IRB/IEC 审查。

(b) 申办者应确保试验参与者已同意为 3.16.4(a)中列出的目的直接访问源记录（见第 2.8.10(n)节）。

3.17 报告

3.17.1 试验提前终止或暂停

如果试验提前终止或暂停，申办者应及时通知研究者/机构和监管机构终止或暂停的情况及其原因。根据适用法规要求，申办者或研究者/机构也应及时通知 IRB/IEC 并说明终止或暂停的原因。在适当情况下，申办者应向研究者提供关于参与者潜在后续治疗和随访的信息。

3.17.2 临床试验/研究报告

(a) 无论试验是完成还是提前终止，或为监管提交进行中期分析，申办者应确保按照适用法规要求准备并向监管机构提交临床试验报告，包括中期报告。申办者

还应确保上市申请中的临床试验报告符合 ICH E3 标准或其他适用法规要求。（注：ICH E3 规定在某些情况下可接受简略的试验报告。）

(b) 当试验中有协调研究者参与时，应考虑让其作为临床试验报告的签署人（见 ICH E3）。

(c) 一旦试验揭盲且相关分析/结论已完成并最终确定，申办者通常应根据适用法规要求：

(i) 公开发布试验结果；

(ii) 对于盲法试验，向研究者提供其参与者所接受治疗的信息；

(iii) 向研究者提供试验结果。如果向参与者提供试验结果摘要，应使用非技术性的、普通人可理解的且非推广性的语言。

4. 数据管理 – 研究者和申办者

本节为责任方（即研究者和申办者）提供关于适当管理数据完整性、可追溯性和安全性的指导，从而允许准确报告、验证和解释临床试验相关信息。本节应与第 2 节和第 3 节中定义的研究者和申办者相应责任一起阅读，并结合 ICH E8(R1)、ICH E9 和 ICH E9(R1)。

临床试验产生的信息的质量和数量应足以满足试验目标，对试验结果提供信心并支持良好的决策。

确保这种质量的系统和流程的设计和实施应与参与者风险和试验结果可靠性相称。

以下关键流程应涵盖完整的数据生命周期，重点关注数据的重要性，并应按比例实施和适当记录：

(a) 确保保护试验参与者数据保密性的流程；

(b) 管理计算机系统以确保其适用且使用得当的流程；

(c) 保护临床试验基本要素的流程，如随机化、剂量调整和盲法；

(d) 支持关键决策的流程，如分析前的数据定稿、揭盲、分析数据集分配、临床试验设计变更，以及在适用情况下 IDMC 等的活动。

4.1 数据管理中的盲法保护

4.1.1 维护盲法的完整性在系统设计、用户账户管理、数据处理相关责任委派、研究中心数据访问权限、数据传输、计划揭盲前的数据库审查以及试验各适当阶段的统计分析方面尤为重要。

4.1.2 所有相关方应根据方案定义并记录访问非盲信息的角色、职责和程序；这些信息也可包含在数据管理计划、统计分析计划或其他试验特定计划/说明和研究中心人员授权记录中。例如，在盲法试验中，参与试验操作并直接或间接与研究中心人员互动的申办者员工或服务提供商不应访问揭盲信息，除非试验设计要求（如使用非盲监查员）。

4.1.3 在这种情况下，应实施适当的缓解策略，以降低无意中揭露盲法研究中心人员盲态的风险。

4.1.4 揭盲的可能性应作为盲法试验风险评估的一部分。任何计划内或计划外揭盲，包括意外或紧急揭盲，都应记录。任何计划外揭盲都应评估其对试验结果的影响，并采取适当措施。

4.2 数据生命周期要素

应建立涵盖完整数据生命周期的程序。

4.2.1 数据采集

(a) 当纸质记录或电子健康记录中的数据手动转录到计算机系统（如数据采集工具）时，数据验证的需求和程度应考虑数据的重要性。

(b) 从任何来源获取的数据，包括直接在计算机系统（如数据采集工具）中采集的数据，都应附有相关元数据。

(c) 在数据采集点，应根据风险考虑实施自动数据验证检查以提出数据质疑，其实施应受控并记录。

4.2.2 相关元数据，包括稽查跟踪

责任方用于实施、评估、访问、管理和审查与高重要性数据相关的元数据的方法应包括：

(a) 评估系统可用的元数据类型和内容，以确保：

(i) 计算机系统维护用户账户创建、用户角色和权限变更以及用户访问的日志；

(ii) 系统设计应允许以记录初始数据输入和任何后续更改或删除的方式进行数据更改，在适当情况下包括更改原因；

(iii) 系统除记录直接数据输入/更改外，还应记录和维护工作流程操作。

(b) 确保稽查跟踪、报告和日志不被禁用。除特殊情况外（如参与者个人信息被无意包含在数据中），稽查跟踪不应被修改，且仅在保留此类操作和理由记录的情况下才能修改；

(c) 确保稽查跟踪和日志可解释且能支持审查；

(d) 确保数据输入或传输的日期和时间自动捕获是明确的（如协调世界时(UTC)）；

(e) 确定哪些已识别的元数据需要审查和保留。

4.2.3 数据和元数据审查

应建立试验特定数据、稽查跟踪和其他相关元数据的审查程序。这应是一项计划性活动，其范围和性质应基于风险，适应个别试验并根据试验期间的经验进行调整。

4.2.4 数据更正

应有流程来更正可能影响试验结果可靠性的数据错误。更正应归属于进行更正的人员或计算机系统，有理由支持，并由原始输入时间附近的源记录支持，且应及时执行。

4.2.5 数据传输、交换和迁移

应建立经验证的流程和/或其他适当流程（如核对），以确保在计算机系统之间传输的电子数据（包括相关元数据）保持其完整性并保护其机密性。数据交换/传输过程或系统迁移应有文档记录以确保可追溯性，并应适当实施数据核对以避免数据丢失和非预期修改。

4.2.6 分析前数据集的最终确定

(a) 应定义用于中期和最终分析的充分质量数据，通过实施及时可靠的数据采集、验证、确认、审查和纠错流程来实现，并在可能的情况下纠正对试验参与者安全和/或试验结果可靠性有重要影响的遗漏。

(b) 分析前确定数据集的活动应按照预先规定的程序确认和记录。这些活动可能包括已输入数据和数据集的核对或相关数据库的核对、数据错误纠正，在可能情况下处理遗漏、医学编码以及不依从问题（包括方案偏离）的汇编和影响评估。

(c) 数据提取和数据分析集的确定应按照计划的统计分析进行，并应记录。

4.2.7 保留和访问

试验数据和相关元数据的归档方式应允许检索和可读性，并在整个保留期间防止未经授权的访问和更改。

4.2.8 销毁

当根据适用法规要求不再需要时，可以永久销毁试验数据和元数据。

4.3 计算机系统

如第 2 节和第 3 节所述，申办者、研究者和其他方关于临床试验中使用的计算机系统的责任应明确并记录。

责任方应确保为其开发临床试验计算机系统的人员了解预期用途和适用的监管要求。

建议在相关情况下让目标参与者群体和医疗专业人员代表参与系统设计，以确保计算机系统适合目标用户群体使用。

4.3.1 计算机系统使用程序

应建立文档化程序，确保在临床试验中适当使用计算机系统进行与数据采集、处理和管理相关的基本活动。

4.3.2 培训

责任方应确保使用计算机系统的人员接受适当的使用培训。

4.3.3 安全性

(a) 在整个数据生命周期中应管理试验数据和记录的安全性。

(b) 责任方应确保计算机系统实施并维护安全控制。这些控制应包括用户管理和持续措施，以防止、检测和/或缓解安全漏洞。应考虑用户认证要求和密码管理、防火墙设置、防病毒软件、安全补丁、系统监控和渗透测试等方面。

(c) 责任方应维护充分的数据备份。

(d) 程序应涵盖以下内容：系统安全措施、数据备份和灾难恢复，以确保防止未经授权的访问和数据丢失。此类措施应定期测试（如适用）。

4.3.4 验证

(a) 责任方负责系统在其整个生命周期中的验证状态。计算机系统验证方法应基于风险评估，考虑系统的预期用途；系统中收集/生成、维护和保留的数据/记录的目的和重要性；以及系统对试验参与者福祉、权利和安全以及试验结果可靠性的潜在影响。

(b) 验证应证明系统符合完整性、准确性和可靠性的既定要求，且其性能与预期用途一致。

(c) 系统应在使用前进行适当验证。后续系统更改应基于风险进行验证，并应根据变更控制程序考虑先前收集的和新的数据。

(d) 可能需要定期审查以确保计算机系统在系统生命周期内保持验证状态。

(e) 标准系统功能和特定于方案的配置和定制（包括自动数据输入检查和计算）都应验证。系统之间的接口也应定义和验证。定制系统、设计为可配置的系统或不需要更改的系统可能需要不同程度的验证。

(f) 在相关情况下，验证程序（直至停用）应涵盖以下内容：系统设计、系统要求、功能测试、配置、发布、设置、安装和变更控制。

(g) 责任方应确保计算机系统经验证适合在试验中使用，包括由其他方开发的系统。他们应确保维护和保留验证文档。

(h) 验证通常应包括定义系统要求和规格及其测试，以及相关文档，以确保系统适合在试验中使用，特别是对于关键功能，如随机化、给药和剂量调整和减少，以及终点数据的收集。

(i) 任何未解决的问题都应得到证明，并且在相关情况下，在系统继续使用之前和/或期间，应通过缓解策略解决从此类问题中识别的风险。

4.3.5 系统发布

试验特定系统（包括由方案修订导致的更新）仅应在收到与该研究中心相关的临床试验的所有必要批准后，才能为各研究中心实施、发布或激活。

4.3.6 系统故障

应建立应急程序，以防止对参与者安全、试验决策或试验结果至关重要的数据丢失或无法访问。

4.3.7 技术支持

(a) 在适当情况下，应建立机制（如帮助台支持）以记录、评估和管理计算机系统问题（如用户提出的），并应定期审查这些累积问题以识别重复和/或系统性问题。

(b) 应根据缺陷和问题的严重程度解决它们。高严重性问题应及时解决。

4.3.8 用户管理

(a) 访问控制是临床试验中使用的计算机系统的组成部分，用于将系统访问限制为授权用户并确保可归属到个人。安全措施的选择应确保实现预期的安全性。

(b) 应建立程序，确保根据用户的职责和功能、盲法安排和用户所属组织适当分配用户访问权限。不再需要时应撤销访问权限。在相关情况下，应建立流程以确保定期审查用户访问权限以及分配的角色和权限。

(c)授权用户和访问权限应清晰记录、维护和保留。这些记录应包括用户角色、访问权限的任何更新以及授予访问权限的时间（例如，时间戳）。

Let me provide a translation of this text about the Investigator's Brochure (IB):

附录 A. 研究者手册

A.1 引言

研究者手册(IB)是一份关于研究产品在人体受试者研究中相关的临床和非临床数据的汇编。其目的是为研究者和其他参与试验的人员提供信息，以帮助他们理解方案中许多关键特征的原理并确保其遵从性，例如剂量、给药频率/间隔、给药方法和安全性监测程序。

A.1.1 研究者手册的制定

通常，申办方负责确保制定并及时更新 IB。对于研究者发起的试验，研究者-申办方应确定是否可从产品许可/上市许可持有人处获得手册。如果研究产品由研究者-申办方提供，则他们应向研究 site 工作人员提供必要信息。在监管部门允许的情况下，当前的科学信息（如基本产品信息手册，例如产品特性概要、包装说明书或标签）可能是适当的替代选择，前提是其包含与研究产品所有重要方面相关的最新、全面和详细信息。如果对已获批准的药品进行新用途（即新适应症）研究，则应制定专门用于该新用途的 IB，除非有理由只使用一份 IB。IB 应至少每年审查一次，并按照申办方的书面程序在必要时进行修订。根据开发阶段和相关新信息的产生情况，可能需要更频繁的修订。某些相关新信息可能非常重要，需要在纳入修订的 IB 之前就通知研究者，并可能需要通知伦理委员会(IRBs/IECs)和/或监管部门。

A.1.2 参考安全性信息和风险-获益评估

IB 中包含的参考安全性信息(RSI)为临床试验中可疑且非预期的严重不良反应(SUSARs)的加速报告提供了重要参考点。该 RSI 应包括不良反应列表，包括其

发生频率和性质的信息。该列表应用于确定可疑严重不良反应是否在预期之内，并据此确定是否需要根据适用的监管要求进行加速报告（参见 3.13.2(c)节）。

IB 还为临床试验期间受试者的临床管理提供指导。信息的呈现应该简明、简单、客观、平衡且非促销性，使临床医生或潜在研究者能够理解并对拟议试验的适当性做出自己的无偏见风险-获益评估。因此，应有具有医学资质的人员参与 IB 的制定，但 IB 的内容应由产生所述数据的学科部门批准。

注：原文中脚注 1 指出："就本指南而言，研究产品一词应被视为与药品、药物、医药产品、疫苗和生物制品同义。"

A.2 一般考虑

这些考虑因素概述了研究者手册中应包含的最低信息要求。可以预见，可用信息的类型和范围将随研究产品的开发阶段而变化。

研究者手册应包括：

A.2.1 标题页

应提供申办方名称、每种研究产品的标识（即研究编号、化学名称或已批准的通用名称，以及在法律允许且申办方期望的情况下的商品名），以及发布日期。建议同时提供版本号以及所取代版本的编号和日期，还应注明该版本所含数据的截止日期。在适当情况下，可包含签名页。

A.2.2 保密声明

申办方可能希望包含一份声明，指示研究者和其他接收者将研究者手册作为保密文件处理，仅供研究者/机构、研究现场工作人员、监管部门和伦理委员会(IRB/IEC)使用。

A.3 研究者手册的内容

研究者手册应包含以下章节，在适当情况下，每个章节末尾应包含文献参考（出版物或报告）：

A.3.1 目录

A.3.2 摘要

应提供简短摘要（最好不超过两页），重点突出与研究产品临床开发阶段相关的重要物理、化学、药学、药理学、毒理学、药代动力学、代谢和临床信息。

A.3.3 引言

应提供简短的介绍性说明，包含研究产品的化学名称（以及已批准时的通用名和商品名）；所有活性成分；研究产品的药理学分类及其在该类别中的预期地位（如优势）；进行研究产品研究的理由；以及预期的预防、治疗或诊断适应症。最后，介绍性说明应提供评估研究产品所遵循的总体方法。

A.3.4 物理、化学和药学性质及配方

应描述研究产品物质（包括化学和/或结构式），并简要总结相关的物理、化学和药学性质。

为了在试验过程中采取适当的安全措施，应描述将使用的配方（包括辅料），如果与临床相关，还应说明其合理性。还应提供剂型的储存和处理说明。

应提及与其他已知化合物的任何结构相似性。

A.3.5 非临床研究

引言

应以摘要形式提供所有相关的非临床药理学、毒理学、药代动力学和研究产品代谢研究的结果。该摘要应说明所用方法、结果以及讨论研究发现与所研究产品的相关性及可能对人体的不良和非预期影响。

如已知/可获得，所提供的信息可包括以下方面：

- 试验物种
- 每组动物的数量和性别
- 单位剂量（如毫克/千克(mg/kg)）
- 给药间隔
- 给药途径
- 给药持续时间
- 系统分布信息
- 暴露后随访持续时间
- 结果，包括以下方面：
  - 药理或毒性效应的性质和频率
  - 药理或毒性效应的严重程度或强度
  - 效应出现时间
  - 效应可逆性

- 效应持续时间
- 剂量反应关系

应尽可能使用表格格式/列表以提高表述的清晰度。

以下各节应讨论研究中最重要的发现，包括观察到的效应的剂量反应关系、与人体的相关性以及需要在人体中研究的任何方面。如适用，应比较同一动物物种中的有效剂量和无毒性剂量（即应讨论治疗指数）。应说明这些信息与建议人体给药的相关性。在可能的情况下，应基于血液/组织水平或人体等效剂量进行比较，而不是基于 mg/kg。

(a) 非临床药理学

应包含研究产品及其重要代谢物（如适用）在动物中的药理学特性总结。该总结应包含评估潜在治疗活性的研究（如疗效模型、受体结合和特异性）以及评估安全性的研究（如评估预期治疗效果以外的药理作用的特殊研究）。

(b) 动物体内药代动力学和产品代谢

应提供所有研究物种中研究产品的药代动力学、生物转化和处置的总结。对研究结果的讨论应涉及研究产品及其代谢物的吸收、局部和系统生物利用度，以及它们与动物物种药理学和毒理学发现的关系。

(c) 毒理学

应在以下适当标题下描述在不同动物物种中进行的相关研究中发现的毒理学效应总结：

- 单次给药毒性
- 重复给药毒性
- 遗传毒性
- 致癌性
- 生殖和发育毒性
- 局部耐受性
- 其他毒性研究

A.3.6 人体效应

引言

应提供研究产品在人体中已知效应的全面讨论，包括药代动力学、代谢、药效学、剂量反应关系、安全性、有效性和其他药理活性的信息。在可能的情况下，应提供每个已完成的临床试验和正在进行的可能提供安全性评估信息的临床试验的中期结果总结。还应提供临床试验以外的研究产品使用结果信息，如上市经验。

(a) 人体药代动力学和产品代谢

应提供研究产品药代动力学信息的总结，如有可能，包括以下内容：

- 药代动力学（包括适当的代谢、吸收、血浆蛋白结合、分布和消除）
- 研究产品的生物利用度（如可能，使用参考剂型的绝对和/或相对生物利用度）
- 人群亚组（如性别、年龄和器官功能受损）
- 相互作用（如产品-产品相互作用和食物影响）
- 其他药代动力学数据（如临床试验中进行的人群研究结果）

(b) 安全性和有效性

应提供有关研究产品（包括适当的代谢物）的安全性、药效学、有效性和剂量反应关系的信息总结，这些信息来自于此前在人体（健康志愿者和/或患者）中进行的试验。应讨论这些信息的意义。在完成多个临床试验的情况下，按适应症在亚组中对多个试验的安全性和有效性进行总结可能会提供清晰的数据呈现。所有临床试验（包括所有研究适应症）的不良药物反应的表格总结，包括其频率和性质的信息将很有用。应讨论不同适应症或亚组之间不良药物反应模式/发生率的重要差异。

研究者手册应描述基于研究产品和相关产品先前经验可能预期的风险和不良药物反应。还应描述作为产品研究使用一部分的预防措施或特殊监测。

(c) 上市经验

研究者手册应确定研究产品已上市或获批的国家。应总结上市使用中产生的任何重要信息（如配方、剂量、给药途径、不良药物反应）。研究者手册还应确定所有未获得上市批准/注册或已撤销上市/注册的国家。

A.3.7 数据总结和指导

本节应对非临床和临床数据进行总体讨论，并尽可能总结来自不同来源关于研究产品各个方面的信息。通过这种方式，可以为研究者提供最有信息价值的数据解释，以及对信息对未来临床试验影响的评估。

在适当情况下，应讨论相关产品的已发表报告。这可以帮助研究者预期临床试验中的不良药物反应或其他问题。

本节的总体目标是使研究者清楚理解可能的风险和不良反应，以及临床试验可能需要的具体测试、观察和预防措施。这种理解应基于研究产品可获得的物理、化学、药学、药理学、毒理学和临床信息。还应基于先前的临床和非临床经验以及研究产品的药理学，为临床研究者提供关于识别和治疗可能的过量和不良药物反应的指导。

附录 B. 临床试验方案和方案修订

临床试验应以清晰、简明和可操作的方案来描述。方案的设计应尽量减少不必要的复杂性，并减轻或消除对试验参与者权利、安全和福祉以及数据可靠性的重要风险。方案制定过程应在适当情况下纳入相关利益相关方的意见。在方案中建立适应性，例如，通过包含特定方案条款的可接受范围，可以减少偏差数量，或在某些情况下减少方案修订的需求。这种适应性不应对参与者安全或试验的科学有效性产生不利影响。

更多信息请参考 ICH E8(R1)临床研究的一般考虑，ICH E9 临床试验统计原则和 ICH E9(R1)临床试验统计原则指南关于估计量和敏感性分析的补充。

试验方案的内容通常应包括以下主题，具体可能因试验设计而异。研究机构特定信息可以在单独的方案页面上提供或在单独的协议中说明，以下列出的某些信息可能包含在其他方案引用文件中，如研究者手册。

B.1 一般信息

B.1.1 方案标题、唯一方案识别号和日期。任何修订也应标明修订号和日期。

B.1.2 申办方的名称和地址。

B.1.3 获授权代表申办方签署方案和方案修订的人员姓名和职务。

B.2 背景信息

B.2.1 研究产品的名称和描述。

B.2.2 对可能具有临床意义的非临床研究发现和与试验相关的临床试验的总结。

B.2.3 已知和潜在风险及效益（如果有）对人体受试者的影响总结。

B.2.4 给药途径、剂量、给药方案和治疗期的描述和理由。

B.2.5 声明试验将依据方案、药物临床试验质量管理规范(GCP)和适用的监管要求进行。

B.2.6 研究人群的描述。

B.2.7 与试验相关且为试验提供背景的文献和数据参考。

B.3 试验目标和目的

清晰描述试验的科学目标和目的。如已定义，包括估计量的信息（参见 ICH E9(R1)）。

B.4 试验设计

试验的科学完整性和结果的可靠性主要取决于试验设计。试验设计的描述应包括：

B.4.1 明确说明试验期间要测量的主要终点和次要终点（如果有）。

B.4.2 描述将要进行的试验类型和设计（如双盲、安慰剂对照、平行设计、自适应设计、平台/伞形/篮子设计、具有分散化要素的试验），以及试验设计、程序和阶段的示意图。

B.4.3 描述为最小化/避免偏倚所采取的措施，包括：

(a) 随机化

(b) 盲法

B.4.4 描述研究产品及其剂量和给药方案，包括剂型、包装和标签的描述。

B.4.5 如适用且未在其他地方描述，提供制备（如复溶）和给药说明。

B.4.6 描述事件安排表（如试验访视、干预和评估）。

B.4.7 预期的受试者参与试验的持续时间，以及所有试验期（包括随访，如果有）的顺序和持续时间描述。

B.4.8 描述针对个别受试者、试验部分或整个试验的"终止规则"或"中止标准"以及"剂量调整"或"剂量中断"。

B.4.9 研究产品（包括安慰剂和其他对照品，如果有）的责任程序。

B.4.10 维护治疗随机化代码和破盲程序。

B.5 受试者选择

B.5.1 受试者入选标准。

B.5.2 受试者排除标准。

B.5.3 在适当情况下的预筛选机制和受试者筛选。

B.6 试验干预的中止和受试者退出试验

研究者可以选择让受试者退出试验。相反，受试者可以决定退出试验或停止研究产品治疗（见 2.8.10(l)、2.8.10(m)和 2.9.1 节）。方案应规定：

(a) 何时以及如何让受试者退出试验/研究产品治疗；

(b) 对退出/中止的受试者收集的数据类型和时间，包括根据适用的监管要求处理数据的过程；

(c) 是否以及如何替换受试者；

(d) 对已中止使用研究产品的受试者的随访。

B.7 受试者的治疗和干预

B.7.1 要施用的治疗，包括所有产品的名称、剂量、给药计划、剂量调整标准、给药途径/方式和治疗期，包括试验每个研究产品治疗/试验治疗组/试验臂的受试者随访期。

B.7.2 试验前和/或试验期间允许（包括合并用药和救援用药）和不允许使用的药物/治疗。

B.7.3 监测受试者治疗依从性的策略。

B.8 有效性评估

B.8.1 如适用，规定有效性参数。

B.8.2 评估、记录和分析有效性参数的方法和时间。如果使用任何试验相关委员会（如独立数据监测委员会(IDMC)/裁定委员会）来评估有效性数据，应在方案或单独文件中描述委员会的程序、时间和活动。

B.9 安全性评估

B.9.1 规定安全性参数。

B.9.2 记录和评估安全性参数的方法、范围和时间。如果使用任何试验相关委员会（如 IDMC）来评估安全性数据，应在方案或单独文件中描述程序、时间和活动。

B.9.3 获取、记录和报告不良事件的程序。

B.9.4 不良事件和其他事件（如妊娠）后对受试者随访的类型和持续时间。

B.10 统计学考虑

B.10.1 描述将采用的统计方法，包括任何计划的期中分析的时间和目的，以及试验终止的统计标准。

B.10.2 计划入组的受试者数量和样本量选择的理由，包括对试验效能的考虑或计算以及临床理由。

B.10.3 将使用的显著性水平或贝叶斯设计中后验概率的成功阈值。

B.10.4 计划分析中将包括的受试者选择，所采用统计方法的描述以及处理中间事件和缺失、未使用和虚假数据的程序。这些应与目标估计量（如已定义）保持一致（见 ICH E9(R1)）。

B.10.5 声明统计分析计划的任何偏离将在临床试验报告中描述和说明理由。

B.11 直接获取源记录

申办方应确保在方案或其他文件协议中规定，研究者/机构/服务提供商将允许与试验相关的监查、稽查、监管检查，并根据适用的监管要求，接受伦理委员会(IRB/IEC)的审查，提供对源记录的直接访问。

B.12 质量控制和质量保证

B.12.1 描述试验中已识别的关键质量因素、相关风险和风险缓解策略，除非在其他地方有文档记录。

B.12.2 总结作为临床试验质量控制过程一部分的监查方法。

B.12.3 描述处理不符合方案或 GCP 的过程。

B.13 伦理

描述与试验相关的伦理考虑。

B.14 数据处理和记录保存

B.14.1 规定要收集的数据和收集方法。必要时，额外细节应包含在临床试验相关文件中。

B.14.2 识别直接记录到数据采集工具中（即无事先书面或电子记录）并被视为源记录的数据。

B.14.3 声明应根据适用的监管要求保存记录。

B.15 资金和保险

资金和保险，如果未在单独协议中说明。

B.16 发表政策

发表政策，如果未在单独协议中说明。

附录 C. 临床试验实施的必要记录

C.1 引言

C.1.1 在临床试验开始前和进行期间会产生许多记录。所产生和维护的记录的性质和范围取决于试验设计、其实施、风险相称方法的应用以及该记录对试验的重要性和相关性。

C.1.2 确定哪些记录是必要的将基于本附录中指南的考虑。

C.1.3 必要记录允许并有助于评估试验的实施是否符合研究者和申办方的药物临床试验质量管理规范(GCP)和适用的监管要求，以及所产生结果的可靠性。必要记录用作研究者监督和申办方监督（包括监查）试验的一部分。这些记录被申办方的独立稽查功能和监管机构检查期间用于评估试验实施和试验结果的可靠性。某些必要记录也可能根据适用的监管要求由伦理委员会(IRB/IEC)审查。研究者/机构应能够获取并维护在试验开始前和进行期间由研究者/机构产生的必要记录，并根据适用的监管要求保留这些记录。

C.2 必要记录的管理

C.2.1 记录应可识别且进行版本控制（在适当时），并应包括适当的作者、审查者和批准者，以及必要时的日期和签名（电子或实体）。

C.2.2 对于分别由申办方或研究者/机构转移或委托给服务提供商的活动，应做出安排，以便在整个试验期间访问和管理必要记录，并在试验完成后保留这些记录。

C.2.3 这些必要记录应在申办方和研究者/机构各自的记录库中维护或引用。这些记录库可称为试验主文件(TMF)。研究者/机构持有的记录库也可称为研究者现场文件(ISF)。

C.2.4 申办方和研究者/机构应维护必要记录（包括源记录）所在位置的记录。试验期间和归档使用的存储系统（无论使用何种媒介）应提供试验记录的适当识别、版本历史、搜索和检索。

C.2.5 申办方和研究者/机构应确保及时收集和归档必要记录，这可以极大地帮助试验的成功管理。某些必要记录通常应在试验开始前就位，并可能在试验期间随后更新。

C.2.6 申办方和研究者/机构应以确保记录完整、可读和随时可用的方式保留必要记录，并可直接供监管机构、监查员和稽查员要求时访问。对必要记录的更改应可追踪。

C.2.7 申办方和研究者/机构应确保保留履行其职责所需的必要记录。原始记录通常应由产生它们的责任方保留。

C.2.8 为了履行其在试验实施中的职责，申办方和研究者/机构可能需要在试验开始前和进行期间访问或复制彼此的相关必要记录。在试验结束时，各方应保留其必要记录（见 2.12.11 和 3.16.3(a)节）。记录位置可能在试验期间因记录性质而异。例如，研究者可能通过申办方提供的门户访问申办方的相关必要记录（如可疑且非预期的严重不良反应(SUSAR)报告），这些必要记录需要在试验结束时由研究者/机构保留。

C.2.9 当使用副本永久替代原始必要记录时，该副本应满足认证副本的要求。

C.2.10 某些记录通常仅由申办方维护和保留（如仅与申办方活动相关的记录，如数据分析），或仅由研究者/机构保留（如包含受试者机密信息的记录）。某些记录可能由申办方和/或研究者/机构保留。

C.2.11 在有盲法考虑和记录受适用数据保护法律约束时，应仔细考虑记录的共享。关于与服务提供商共享必要记录，见 C.2.2 节。

C.2.12 某些必要记录可能不是特定于某个试验，而是与研究产品、设施或参与运行多个试验的过程和系统（包括计算机系统）相关，并保留在试验特定记录库之外（如研究者手册、主服务协议、标准操作程序、验证记录）。

C.3 试验记录的必要性

C.3.1 评估记录是否必要且必须保留应考虑以下标准。虽然这种评估很重要，但不需要记录。可以使用存储库的结构化内容列表来前瞻性地识别必要记录。必要记录应：

(a) 提交给或由监管机构或伦理委员会(IRB/IEC)发布的文件，包括相关往来函件以及记录监管决定或批准/同意意见的文件；

(b) 试验特定的程序或计划；

(c) 与试验实施和所用流程相关的重要讨论和/或试验相关决定的相关往来函件或会议文档；

(d) 记录相关试验程序实施的文件（如按照数据管理标准操作规程(SOPs)产生的数据库锁定清单）；

(e) 记录各方之间安排和保险/赔偿安排的文件；

(f) 记录符合监管机构要求和批准条件或伦理委员会同意意见的文件；

(g) 记录参与试验批准或实施的任何委员会的组成，以及在适当情况下的职能、往来函件和决定的文件；

(h) 证明试验特定的计算机系统经过验证，非试验特定系统（如临床实践计算机系统）已被评估为适合在试验中预期使用的文件；

(i) 经申办方和/或研究者授权/签署以确认审查或批准的文件；

(j) 在必要时，证明执行重要试验相关活动的人员签名/姓名首字母的文件，例如，完成数据采集工具；

(k) 记录向潜在试验参与者提供的信息，以及适当获得和维护参与者知情同意的文件；

(l) 记录参与试验实施的申办方人员和代表其执行重要试验相关活动的个人通过教育、培训和经验具备资格执行其活动的文件；

(m) 记录研究者和研究者委派执行重要试验相关活动的个人通过教育、培训和经验具备资格执行其活动的文件，特别是当这些活动不属于其正常职责时；

(n) 包含允许适当评估试验实施所需的数据以及相关元数据的文件；

(o) 与申办方或研究者在试验期间对试验参与者安全监督相关的文件，包括申办方与研究者、监管机构和伦理委员会之间的安全报告要求的合规性，以及必要时向试验参与者通报安全信息；

(p) 记录服务提供商具备适当资格执行其委托或转让活动的文件；

(q) 记录试验中使用的实验室活动和其他测试适合其目的的文件；

(r) 记录申办方对研究机构选择和监查以及试验稽查的监督的文件，在适当情况下，提供关于出现的问题/不合规和发现的偏差以及纠正和预防措施实施的信息；

(s) 记录符合方案和/或数据管理和统计分析程序以及任何期中报告和最终报告制作的文件；

(t) 记录生物样本的收集、监管链、处理、分析和保留或销毁的文件；

(u) 提供关于研究产品及其标签的相关信息；

(v) 提供关于研究产品的运输、储存、包装、分发、随机化和盲法的信息；

(w) 在适当情况下，提供从制造商放行到分发、给予试验参与者、退回和销毁或替代处置的研究产品的可追溯性和责任信息；

(x) 提供关于试验中使用的研究产品的身份和质量的信息；

(y) 记录与破盲相关的过程和活动的文件；

(z) 记录试验参与者的招募、试验前筛选和知情同意过程以及其身份和适当的按时间顺序入组的文件；

(aa) 记录试验参与者的存在并证实收集的试验数据的完整性的文件。包括与试验和试验参与者医疗治疗及病史相关的源记录；

(bb) 定义在发生安全漏洞时为保护参与者权利、安全和福祉以及数据完整性而采取的流程/做法。

C.3.2 根据 C.3.1 节中的标准，必要记录表中列出了被认为必要的试验记录，这些记录在产生时应予以保留。

这张表并非详尽的清单，申办方或研究者可能认为其他试验记录也是必要的。

C.3.3

对于必要记录表中列出的某些试验记录，其存在和性质取决于试验设计、试验实施和风险相称的试验管理，可能不会产生。

必要记录表

如果产生这些试验记录，则被视为必要的记录且应予以保留（参见章节 C3.1 和 C3.2）。

注：星号(*)标识那些通常应在试验开始前就位的必要记录（参见章节 C2.5）。

记录类型
研究者手册或基本产品信息手册（如产品特性概要、包装说明书或标签）*
已签署的方案*和试验期间的后续修订

记录类型
伦理委员会对提供给伦理委员会的信息的有日期的、记录在案的批准/同意意见*
伦理委员会的组成*
监管机构对方案*和试验期间后续修订的授权、批准和/或通知（如需要）
已完成的签署并注明日期的知情同意书
已完成的受试者识别代码清单和入组日志
• 研究者向申办方通报严重不良事件(SAEs)和相关报告（如需要） • 申办方和/或研究者向监管机构和伦理委员会通报可疑且非预期的严重不良反应(SUSARs)和其他安全信息（如需要） • 申办方向研究者通报安全信息（如需要）
向伦理委员会和监管机构提交的期中或年度报告（如需要）
源记录
数据采集工具中的数据和相关元数据（包括数据更正文档）
向伦理委员会和监管机构提交的最终报告（如需要）
期中（如适用）和最终临床试验报告
提供给研究者和/或伦理委员会的数据采集工具样本（如病例报告表(CRFs)、日记、临床结果评估，包括患者报告的结果）*
提供给试验参与者的信息样本* • 知情同意材料（包括所有适用的翻译）

必要记录表

如果产生这些试验记录，则被视为必要记录且应予以保留（参见章节 C3.1 和 C3.2）。

注：星号(*)标识那些通常应在试验开始前就位的必要记录（参见章节 C2.5）。

记录类型
• 任何其他文档信息（如研究产品或设备使用说明）
• 受试者招募广告
试验财务方面各方之间的安排*
保险声明*
相关方之间签署的协议*，例如： • 研究者/机构和申办方 • 研究者/机构和服务提供商 • 申办方和服务提供商 • 申办方和 IDMC 和/或裁定委员会成员
记录执行重要试验相关活动的服务提供商的选择、评估*和监督的文件
证明参与进行试验的研究者和助理研究者资格的相关文件（如简历）*
试验特定的培训记录*
研究者委派试验相关活动的文件*
记录签名和姓名首字母的签名表，除非仅使用电子签名（研究者和研究者委派的个人）*（可与上述委派文件合并）
方案中包含的医疗/实验室/技术程序和/或检测的正常值/范围*
认证或资格认可或其他文件，包括验证（如需要）以确认试验实施期间使用的医疗/实验室/技术程序/检测的适用性*
体液/组织样本的收集、处理和运输文件

记录类型
体液/组织样本储存条件文件
试验结束时保留的体液/组织样本记录
贴在研究产品容器上的标签样本
研究产品和试验相关材料的处理说明（如果未包含在方案或研究者手册中），例如药房手册*
研究产品和试验相关材料的运输记录*
运输的研究产品的分析证书*
研究机构的研究产品责任记录

必要记录表

如果产生这些记录，则被视为必要记录且应予以保留（参见章节 C3.1 和 C3.2）。

注：星号(*)标识那些通常应在试验开始前就位的必要记录。

记录类型
研究产品储存条件的文件记录，包括运输期间的条件
研究者现场研究产品重新标签的记录
研究产品销毁或替代处置的文件记录
盲法试验的紧急揭盲程序*
主随机化清单*
重要试验特定系统的使用说明（例如，交互式响应技术(IRT)用户手册，电子病

记录类型
例报告表(eCRF)手册）*
证明重要试验活动所用设备适用性的记录（如维护和校准）*
治疗分配和揭盲文件
已完成的参与者筛选日志
现场监查报告（包括现场选择、*启动*、常规和结束访视）
集中监查报告
违规记录和报告，包括方案偏差以及纠正和预防措施
相关沟通和会议的文件记录
稽查证书
与数据分析定稿相关的文件（如查询解决方案、SAE 协调、质量控制报告、编码完成输出数据集）
试验特定计算机系统验证的文件记录（如规格说明、测试验证报告、变更控制）*
评估重要试验特定计算机系统适用性的文件记录（如计算机化系统）*
与统计考虑和分析相关的文件（如样本量计算*、分析集决策、分析数据集、分析程序、质量控制记录和输出）
试验特定计划（如风险管理、*监查*、安全、*数据管理*、数据验证*以及统计分析）和程序
IDMC/裁定委员会的程序*、会议记录和提交材料

术语表

不良事件和不良反应相关定义：

不良事件(AE)：接受研究产品的试验参与者出现的任何不良医疗事件。该不良事件与治疗不一定有因果关系。

不良药物反应(ADR)：

- 在新研究产品或其新用途的上市前临床经验中（特别是在尚未确定治疗剂量时）：任何剂量的药品引起的不良和非预期反应，如体征（如实验室结果）、症状或疾病，其中药品与不良事件之间存在合理的因果关系可能性。不良药物反应与研究产品的相关性确定程度会有所不同。如果 ADR 被高度确定怀疑与药品相关，应将其纳入参考安全信息(RSI)和/或研究者手册(IB)中。
- 对于已上市药品：在用于人类预防、诊断或治疗疾病或改变生理功能的正常剂量下发生的有害和非预期的药物反应。

（参见 ICH E2A《临床安全性数据管理：加速报告的定义和标准》）

严重不良事件(SAE)：任何剂量下被认为严重的不良医疗事件，如果：

- 导致死亡
- 危及生命
- 需要住院治疗或延长现有住院时间
- 导致持续或显著的残疾/功能丧失
- 导致先天性异常/出生缺陷

（参见 ICH E2A）

可能不会立即危及生命或导致死亡或住院，但可能危及参与者或需要干预以防止严重后果的重要医疗事件（参见 ICH E2A 和 E19）通常应被视为严重。

可疑且非预期的严重不良反应(SUSAR)：符合三个标准的不良反应：可疑的、非预期的和严重的。

- 可疑：有合理可能性认为该药物导致了不良药物反应。
- 非预期：其性质或严重程度与适用的产品信息不一致的不良反应（如研究者手册或根据适用监管要求的替代文件；参见 RSI）。
- 严重：参见上述 SAE。

协议

描述两个或多个方之间关于活动的委托或转让、分配和/或共享的详细安排，以及适当时的财务事项的文件或文件集。这可以采用合同形式。方案可作为协议的基础。

适用的监管要求

任何涉及研究产品临床试验开展的法律和法规。

知情同意

未成年人参与临床试验的确认性同意。不表达同意或不同意不应被解释为知情同意。

稽查

由申办方、服务提供商（包括合同研究组织(CRO)）或机构进行的系统性和独立的试验相关活动和记录检查，以确定所评估的试验相关活动是否按照方案、适用的标准操作规程(SOPs)、药物临床试验质量管理规范(GCP)和适用的监管要求进行，且数据是否被准确记录、分析和报告。

稽查证书

稽查员确认已进行稽查的声明。

稽查报告

描述稽查实施和结果的记录。

稽查追踪

通过捕获与信息和数据收集相关的行为（手动或自动）细节，以及在适用时计算机系统中活动的元数据记录，允许对事件过程进行适当评估。稽查追踪应显示活动、初始输入和对数据字段或记录的更改，由谁进行，何时进行，以及在适用时进行的原因。在计算机系统中，稽查追踪应是安全的、计算机生成的且带有时间戳的。

盲法/遮盖

一项使试验的一方或多方不知晓治疗分配的程序。单盲通常指参与者不知情，双盲通常指参与者和研究者以及适当时其他研究者现场工作人员或申办方工作人员不知晓治疗分配。

病例报告表(CRF)

一种数据采集工具，旨在记录研究者向申办方报告的每位试验参与者的方案要求信息（参见数据采集工具）。

认证副本

经验证（即通过带日期的签名或通过验证过的流程生成）具有与原始记录相同信息的副本（无论使用何种媒介），包括相关元数据（如适用）。

临床试验

任何旨在发现或验证研究产品的临床、药理和/或其他药效学作用；和/或识别研究产品的任何不良反应；和/或研究研究产品的吸收、分布、代谢和排泄，以确定其安全性和/或有效性的人体参与者干预性研究。

临床试验/研究报告(CSR)

对在人体参与者中进行的任何研究产品试验的文档描述，其中临床和统计描述、展示和分析完全整合到一份报告中（参见 ICH E3《临床研究报告的结构和内容》）。

对照品

在临床试验中用作参考的研究或已获准的药品（即活性对照）、安慰剂或标准治疗。

依从性（与试验相关）

遵守试验相关要求、GCP 要求和适用的监管要求。

保密性

防止向未经授权的个人披露申办方的专有信息或参与者的身份或其机密信息。

协调研究者

在多中心试验中被指派负责协调不同研究者现场的研究者之间协调工作的研究者。

计算机系统验证

一个建立和记录计算机系统的特定要求能够从设计到系统退役或过渡到新系统期间持续满足的过程。验证方法应基于风险评估，考虑系统的预期用途以及系统对试验参与者保护和试验结果可靠性的潜在影响。

合同研究组织(CRO)

参见服务提供商。

数据采集工具(DAT)

根据方案设计的纸质或电子工具，用于从临床试验中的数据源收集数据和相关元数据，并向申办方报告数据。数据源可以是人（如参与者或试验人员）、机器（如可穿戴设备和传感器）或已进行系统间电子数据传输的计算机系统（如从电子健康记录或实验室系统提取数据）。

数据采集工具的示例包括但不限于 CRF、交互式响应技术(IRT)、临床结果评估(COA)，包括患者报告结果(PRO)和可穿戴设备，不论使用何种媒介。

数据完整性

数据完整性包括数据满足可归属、清晰、同期、原始、准确、完整、安全和可靠等关键标准的程度，使数据适合其目的。

直接访问

允许检查、分析和验证对临床试验评估重要的记录，可以在现场或远程进行。任何具有直接访问权限的方（如国内外监管机构、申办方的监查员和稽查员）都应在适用监管要求的约束下采取合理预防措施，维护参与者身份和其数据以及申办方专有信息的机密性。

必要记录

必要记录是与临床试验相关的任何格式的文件和数据（及相关元数据），这些记录有助于试验的持续管理，并共同允许评估所使用的方法、影响试验的因素和试验进行期间采取的行动，以确定所产生的试验结果的可靠性，并验证试验是否按照 GCP 和适用的监管要求进行（参见附录 C）。

药物临床试验质量管理规范(GCP)

一个用于计划、启动、执行、记录、监督、评估、分析和报告临床试验的标准，该标准确保数据和报告的结果可靠，并保护试验参与者的权利、安全和福祉。

公正见证人

独立于试验的人员，不会受到试验相关人员的不当影响，在参与者或其合法代表无法阅读时出席知情同意过程，并阅读知情同意书和提供给或读给参与者和/或其合法代表的任何其他文档信息。

独立数据监查委员会(IDMC)

申办方可能设立的独立数据监查委员会（如数据安全监查委员会），定期评估临床试验的进展、安全性和相关有效性数据，并向申办方建议是否继续、修改或停止试验。

知情同意

参与者或其合法代表在被告知并有机会讨论与参与者参与决定相关的试验所有方面后，自愿确认其愿意参与试验的过程。可以使用各种方法提供信息和讨论试验。这可能包括，例如，以不同格式提供文本、图像和视频，并使用电话或视频会议与研究者现场工作人员交流。知情同意通过书面（纸质或电子）、签署并注明日期的知情同意书进行记录。在适当时可以考虑远程获取同意。

检查

监管机构对被认为与临床试验相关的文件、设施、记录和任何其他资源进行官方审查的行为，这些资源可能在研究者现场、申办方和/或服务提供商（包括 CRO）的设施，或监管机构认为适当的其他场所进行访问。检查的某些方面可以远程进行。

机构

任何进行临床试验的公共或私营实体或机构或医疗或牙科组织。

机构审查委员会(IRB)/独立伦理委员会(IEC)

由医疗专业人员和非医疗成员组成的独立机构（审查委员会或委员会，可以是机构的、地区的、国家的或超国家的），其职责是确保保护参与试验的人类参与者的权利、安全和福祉，并通过审查和批准/提供关于试验方案、研究者适合性、设施以及用于获取和记录试验参与者知情同意的方法和材料的意见等方式，为该保护提供公众保证。IRBs/IECs 的法律地位、组成、功能、运作和监管要求可能因国家而异，但应允许 IRB/IEC 按照本指南所述的 GCP 行事。

期中临床试验/研究报告

基于试验过程中进行的分析得出的中期结果及其评估的报告。

研究产品

在临床试验中被测试或用作参考的活性成分或安慰剂的药物形式，包括已获得上市许可的产品，当其使用或组装（配制或包装）方式与批准形式不同，或用于未

批准的适应症，或用于获取已批准用途的进一步信息时。研究产品应被视为与药物、药品、医药产品、疫苗和生物制品同义。

研究者

负责临床试验实施的人员，包括在试验进行期间对其负责的试验参与者。如果试验由一组人员进行，研究者是该团队的负责人，可称为主要研究者。当本指南提及研究者/机构时，描述了在某些地区可能适用于研究者和/或机构的期望。在适用监管要求要求的情况下，"研究者"应理解为"研究者和/或机构"。

研究者手册(IB)

关于研究产品的临床和非临床数据的汇编，这些数据与人类参与者研究产品的研究相关（参见附录 A）。

研究者现场

在研究者/机构监督下进行和/或协调试验相关活动的地点。

合法代表

根据适用法律授权代表潜在参与者同意其参与临床试验的个人或法人或其他机构。当合法代表代表潜在参与者提供同意时，与同意过程相关的活动（和重新同意，如适用）以及在相关情况下与本指南所述的撤回同意相关的活动适用于参与者的合法代表。

元数据

理解给定数据元素所需的上下文信息。元数据是描述、解释或以其他方式使数据更容易检索、使用或管理的结构化信息。就本指南而言，相关元数据是那些需要允许对试验实施进行适当评估的元数据。

监查

监督临床试验进展并确保临床试验按照方案、SOPs、GCP 和适用监管要求进行、记录和报告的行为。

监查计划

描述试验监查策略、方法、职责和要求的文件。

监查报告

现场和/或集中监查活动后的文档报告。

多中心试验

按照单一方案但在多个研究者现场进行的临床试验。

非临床研究

不在人类参与者身上进行的生物医学研究。

方案

描述试验目标、设计、方法、统计考虑和组织的文件。方案通常也提供试验的背景和理由，但这些可以在其他方案参考文件中提供。在整个 ICH GCP 指南中，"方案"一词指方案和方案修订。

方案修订

对方案变更的文档描述。

质量保证(QA)

为确保试验的执行以及数据的生成、文档记录和报告符合 GCP 和适用监管要求而建立的所有计划性和系统性行动。

质量控制(QC)

为验证试验相关活动的质量要求已得到满足而采取的操作技术和活动。

随机化

在将参与者分配到接受不同治疗的组时，有意引入偶然性因素以减少偏倚的过程。

参考安全信息(RSI)

包含在临床试验中给予参与者的研究产品预期出现的累积 ADR 清单。RSI 包含在研究者手册或根据适用监管要求的替代文件中。有关 RSI 的更多信息，请参见 ICH E2F 开发安全性更新报告。

监管机构

具有监管权力的机构，包括审查提交的方案和临床数据以及进行检查的机构。这些机构有时被称为主管部门。

服务提供商

为申办方或研究者提供用于完成试验相关活动服务的个人或组织（商业、学术或其他）。

签名

个人根据适用监管要求和/或实践执行、采用或授权的独特标记、符号或条目，用以表示意愿表达并允许对签署人进行认证（即确立高度确定性证明记录由声称的签署人签署）。签名可以是物理的或电子的。

源记录

原始文件或数据（包括相关元数据）或原始文件或数据的认证副本，无论使用何种媒介。这可能包括试验参与者的医疗/健康记录/笔记/图表；试验参与者提供/输入的数据（如电子患者报告结果(ePROs)）；参与临床试验的药房、实验室和其他设施的医疗保健专业人员记录；以及来自自动化仪器的数据，如可穿戴设备和传感器。

申办方

对临床试验的启动、管理和资金安排负责的个人、公司、机构或组织。在监管要求允许的情况下，临床试验可以有一个或多个申办方。所有申办方都具有本指南中规定的申办方责任。根据适用的监管要求，申办方可以通过书面协议确定各自的责任。如果书面协议未指明某项责任归属于哪个申办方，则该责任由所有申办方承担。

申办者-研究者

既发起又独自或与他人一起进行临床试验的个人，并在其直接指导下向参与者施用、分发或使用研究产品。该术语不包括个人以外的任何人（例如，该术语不包括公司或机构）。申办者-研究者的义务包括申办方和研究者的义务。

标准操作规程(SOPs)

为实现特定活动执行的统一性而制定的详细的书面说明。

助理研究者

临床试验团队中由研究者指定并在其监督下执行重要试验相关程序和/或做出重要试验相关决定的任何个人成员（如助理、住院医师、研究员）。

试验参与者

参与临床试验并预期接受研究产品或作为对照的个人。在本指南中，试验参与者和参与者可互换使用。

试验参与者识别代码

分配给每个试验参与者的唯一标识符，用于保护参与者的身份，并在研究者报告不良事件和/或其他试验相关数据时代替参与者姓名使用。

弱势参与者

其参与临床试验的意愿可能受到不当影响的个人，无论是否合理，这种影响可能来自与参与相关的预期利益，或来自层级结构中高级成员在拒绝参与情况下的报复性反应。例如具有等级结构的群体成员，如医学、药学、牙科和护理专业学生；下属医院和实验室人员；制药行业员工；武装部队成员；以及被拘留人员。其他弱势参与者可能包括养老院人员、失业或贫困人员、急诊患者、少数民族群体、无家可归者、游牧民、难民、未成年人和无法给予同意的人。