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

ICH HARMONISED GUIDELINE

GUIDELINE FOR GOOD CLINICAL PRACTICE

E6(R3)

Annex 2

Final version

Adopted on 03 June 2026

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) Annex 2	Endorsement by the Members of the ICH Assembly under *Step 2* and release for public consultation.	06 November 2024
E6(R3)	Endorsement by the Regulatory Members of the ICH Assembly under *Step 4.*	06 January 2025
E6(R3)	Error Correction: Typographical corrections to references in; Section 1.2.5 and 3.16.4	24 October 2025
E6(R3) Annex 2	Endorsement by the Regulatory Members of the ICH Assembly under *Step 4.*	3 June 2026

ICH HARMONISED GUIDELINE

GOOD CLINICAL PRACTICE (GCP)

E6(R3) ANNEX 2

ICH Consensus Guideline

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ANNEX 2

INTRODUCTION

Good Clinical Practice (GCP), as described in ICH E6(R3) Principles and Annex 1, is applicable across clinical trial types, designs and settings, and remains relevant when various operational approaches, design elements and data sources are used in a clinical trial. For simplicity, various operational approaches, design elements and data sources are collectively referred to in this guideline also as methodologies. As clinical trial designs evolve and technological advances occur, the application of GCP should be tailored to the trial design and technologies utilised. In this context, the application of a proportionate risk-based approach (as explained in the Principles and Annex 1) remains relevant and supports the use of evolving trial designs and technologies without compromising the rights, safety and well-being of the participants and the reliability of the trial results. In response to the increased use of various operational approaches, design elements and data sources, ICH E6(R3) Annex 2 provides additional GCP considerations, focusing on trials that incorporate decentralised elements, pragmatic elements and/or real-world data (RWD). Clinical trials may incorporate one or more of these methodologies. Annex 2 is not meant to be comprehensive of all methodologies, recognising that clinical trial ecosystems may continue to evolve, and new approaches, designs and data types may emerge. Considerations included in this Annex may be applied to those evolving methodologies provided they are applied in accordance with local regulatory requirements. This Annex should not be read as an endorsement of any specific methodologies and should be read in conjunction with the Principles and Annex 1.

For the purposes of Annex 2, decentralised elements in a clinical trial are those trial-related activities conducted outside the investigator's location. These may include trial visits and/or protocol-related procedures conducted at the trial participant's home, local healthcare centres or mobile medical units. They also encompass remote interactions, such as video calls or the use of digital health technologies (DHTs) to conduct visits, perform procedures and collect data.

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

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

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

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

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

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

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

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

2. INVESTIGATOR

2.1 Communication with IRB/IEC

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

2.2 Informed Consent Considerations

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

described below for obtaining consent, should be in accordance with applicable regulatory requirements. The informed consent materials and process should be tailored to reflect the various operational approaches, design elements and data sources incorporated in the trial.

2.2.1 Informed consent may be obtained remotely where appropriate. When informed consent is obtained remotely, the investigator should assure themselves of the identity of the participant (or legally acceptable representative where applicable). This may be performed, for example, by verification of an official identification document via a video call. The verification method along with the measures to safeguard data privacy should be pre-specified.

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

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

2.3 Investigational Product Management

Various approaches to investigational product management (i.e., supply, storage, dispensing, administration, return, accountability documentation, destruction or alternative disposition) may be utilised, as appropriate. The investigational product may be dispensed or supplied to the participant or to an appropriate designee (e.g., caregiver, home nurse, local pharmacist) for administration at the participant's location (e.g., participant's home, local healthcare centre) by appropriate parties (e.g., the investigator site staff, the participant, a home nurse or a local pharmacist). These approaches should be arranged and conducted in accordance with applicable regulatory requirements.

2.3.1 The investigator/institution may arrange to send the investigational product to the participant (e.g., to the participant's home) following the sponsor's documented instructions, where applicable. Such arrangements should also comply with applicable regulatory requirements. When shipping investigational products to a participant, the following should be considered:

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

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

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

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

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

2.3.2 Where permitted by applicable regulatory requirements, the sponsor may arrange to send the investigational product to the participant. In such cases:

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

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

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

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

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

2.3.4 The investigator should maintain appropriate oversight of the activities related to investigational product management and should ensure that appropriate documentation is maintained (see Annex 1, section 2.10.4). The level of investigator oversight will depend on a number of factors, including the trial design, characteristics of the investigational product, route and complexity of administration, level of existing knowledge about the investigational product's safety and marketing status (see Annex 1, section 2.10). The activities that should be under the oversight of the investigator include, but are not limited to:

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

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

2.4 Investigator Oversight

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

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

An appropriate level of oversight is context-dependent (e.g., depending on trial characteristics, such as trial design, trial population, investigational product and data sources). An appropriate

level of oversight may range from direct supervision to less intensive oversight, whether in person or via remote communication methods (e.g., video, telephone or email), to only the review of essential records (including source records).

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

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

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

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

In either case mentioned above, the level of investigator oversight should be proportionate to the criticality of data to participant protection and the reliability of the trial results. Regardless of whether healthcare professionals involved in the trial are arranged by the sponsor or investigator, such oversight should ensure that the resulting records meet the relevant requirements of the protocol and thereby ensure reliable trial results, trial participant protection and appropriate decision making.

2.5 Safety Assessment and Reporting

For the safety monitoring of individual trial participants (see Annex 1, section 2.7), the investigator should review and assess information on the health status of participants across the sources of safety-related information. Safety information generated from, for example, home nursing, remote visits, and use of DHTs, should be provided to the investigator in a manner that allows the investigator to make decisions on the care of the participant and ensures participant safety (see Annex 2, section 3.9 and Annex 1, section 3.13.2).

3. SPONSOR

3.1 Engagement and Communication

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

3.1.1 Engaging patients, patient advocacy groups and their communities, as appropriate, can help ensure the successful integration and implementation of the methodologies used in trials. For example, involving patients early in the design of the trial may help to refine the trial design, including ensuring the suitability of DHTs (e.g., mobile applications, wearables) used in trials with decentralised elements, and help address issues related to the logistics of participation. This engagement may also highlight areas where additional training or support may be needed (e.g., digital literacy, physical ability or lack of access to technology that may require the use of alternative approaches, specialised training or the provision of technology).

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

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

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

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

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

3.2 Protocol and Trial Design

Appendix B describes topics that should generally be included in the clinical trial protocol. Additional consideration may need to be given to the protocol and protocol-related documents when utilising various methodologies so that all parties involved in the trial conduct are adequately informed.

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

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

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

data sources or settings. The impact of such data variability should be considered in the trial design and discussed in the protocol or protocol-related documents (e.g., statistical analysis plan).

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

3.2.5 The protocol and, where applicable, protocol-related documents should describe how safety information will be collected from the variety of data sources (e.g., by DHTs, in-person or remote visits), how data and information suggesting a potential safety concern will be identified and made available to the investigator in a timely manner, and what actions should be taken by the investigator in these instances. Such information should be provided to the investigator in a manner that would help inform their decision making (e.g., on eligibility, treatment, continuing participation in the trial and care for the safety of the individual trial participants) (see Annex 2, sections 2.5 and 3.9).

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

3.3 Communication with IRB/IEC

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

3.4 Access to and Use of RWD

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

3.4.1. Access to RWD

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

Individual-level data (pseudonymised for trial use) are datasets or listings capturing data for each individual, usually extracted from source records and structured for statistical analysis and reporting. Pseudonymised data are processed such that a specific individual cannot be identified without collating the data with additional information. Data in source records refer to the data in the original records, such as patient medical records, laboratory reports, imaging files and physician notes, from which individual-level data are derived

(see the glossary term "source records"). Source records are typically not pseudonymised and contain patient-identifying information as well as other information subject to data privacy and protection requirements.

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

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

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

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

3.4.2. Consent and Permission Considerations for RWD

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

a broad manner to allow for potential future research use (i.e., broad consent). In other regions, permission from an IRB/IEC may substitute for obtaining consent for secondary use of data.

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

3.5 Data Considerations

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

3.5.1 RWD Considerations

(a) The sponsor should ensure the fitness for purpose of RWD, which can be described by their reliability and relevance. The term reliability includes accuracy, completeness, provenance and traceability; the term relevance includes the availability of key data elements (e.g., exposure, outcomes, covariates) to answer the specific trial question with the specific method. Attention should be given to the variability in data source, potential bias, generalisability and traceability of RWD. The sponsor should implement procedures that support adequate documentation, data linkage and quality control, while accounting for differences in how RWD are structured, collected and managed across various sources. In selecting RWD sources, sponsors should assess whether the data are appropriate to support the specific trial endpoints and objectives and should weigh the potential benefits against limitations, taking into account the considerations described in 3.5.1(b) below. These considerations should be reflected in trial planning, protocol design and oversight processes.

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

Sponsors should assess whether the RWD source is fit for purpose for the intended use in the trial. In doing so, sponsors should also apply a risk-proportionate approach to the measures used to ensure appropriate data quality, integrity, and governance for the RWD incorporated into the trial. This approach should consider the importance of the data to the trial objectives and the potential impact of data limitations on trial results.

The considerations that may inform the determination of whether a given RWD source is fit for purpose include, but are not limited to, the following:

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

(ii) Lack of standardised timing of data collection and procedures (e.g., the timing and frequency of clinical assessments in RWD are based on clinical practice and may have been influenced by the participant's clinical status;

therefore, the protocol schedule may not match with those available from the RWD).

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

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

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

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

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

(c) Multiple data sources might need to be linked to support the reliability, including completeness of RWD (e.g., linkage of data from EHRs and claims databases or linkage of a RWD source to a mortality database to confirm outcomes). When data are linked, accurate matching to the individual should be assured, and the sponsor should ensure adequate measures to sufficiently protect both data privacy and the reliability of trial results. If data are to be linked, this should be pre-specified in the protocol or protocol-related documents, including how data inconsistencies between different sources will be resolved in a systematic and consistent manner.

3.5.2 *Remote Data Collection Considerations*

(a) Remote data collection in clinical trials (e.g., the use of remote visits and DHTs, extraction of data from EHRs) requires special attention to be paid to data security vulnerabilities (see Annex 1, section 4.3.3), including cybersecurity and data privacy (see Annex 2, section 3.7).

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

3.6 Investigational Product Management

Various approaches to investigational product management (i.e., supply, storage, dispensing, administration, return, accountability documentation, destruction or alternative disposition) may be utilised as appropriate and in accordance with applicable regulatory requirements (see Annex 2, sections 2.3 and 3.8; Annex 1, section 3.15.3).

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

3.6.2 The sponsor may arrange to send the investigational product to the participant (e.g., to the participant's home) in accordance with applicable regulatory requirements. Such shipment should be carried out in accordance with the protocol, and the sponsor should ensure that the shipment process is initiated after being authorised by the investigator. For specific considerations for investigational product shipping to the participant, see Annex 2, section 2.3.1; in addition, see the privacy and confidentiality considerations in Annex 2, section 3.7.

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

3.7 Privacy and Confidentiality Considerations

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

3.8 Sponsor Oversight

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

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

3.9 Safety Assessment and Reporting

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

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

3.9.2 The approach to safety management, including any mitigating actions to safeguard participant safety, and to reporting should be described in the protocol or protocol-related documents (e.g., the safety management plan). This approach should take into account the methodologies used in the trial. Where appropriate, consideration should be given to ICH E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials.