

ICH E6 (R3) GCP Guideline Annex 2 – Step 4 version

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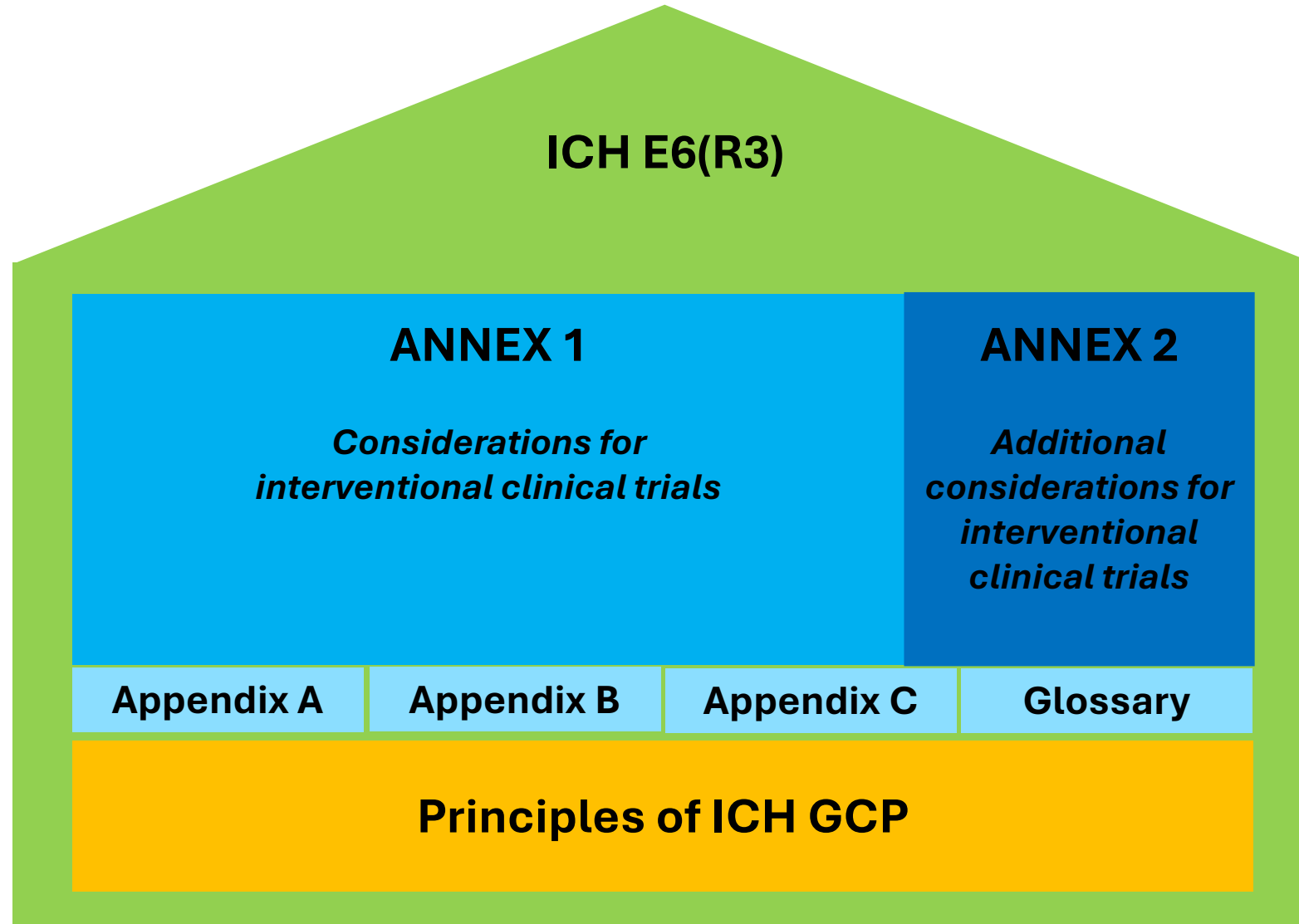
Outline

- Background
- Overview
- IRB/IEC Responsibilities
- Investigator Responsibilities
- Sponsor Responsibilities
- Summary
- References

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ICH E6 (R3) GCP guideline - Overview



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ICH E6 (R3) GCP guideline - Structure

I. INTRODUCTION

II. PRINCIPLES OF ICH GCP

III. ANNEX 1

1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)
2. Investigator
3. Sponsor
4. Data Governance - Investigator and Sponsor

IV. ANNEX 2

Introduction

1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)
2. Investigator
3. Sponsor

APPENDICES

Appendix A. Investigator's Brochure

Appendix B. Clinical Trial Protocol and Protocol Amendment(s)

Appendix C. Essential Records for the Conduct of a Clinical Trial

GLOSSARY

Outline

- Background
- **Overview**
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Annex 2

- Addresses **additional GCP considerations** that arise from various **operational approaches, design elements** and **data sources**, which are collectively referred to in this guideline as '**methodologies**'.
- Has its foundations in the key concepts of **quality by design, fitness for purpose** and **risk proportionality**.
- Does not endorse any specific operational approaches, design elements or data sources.
- Should be **read in conjunction** with the **Principles and Annex 1 of ICH E6 (R3) GCP guideline**..

Annex 2 - Methodologies



Decentralised Elements



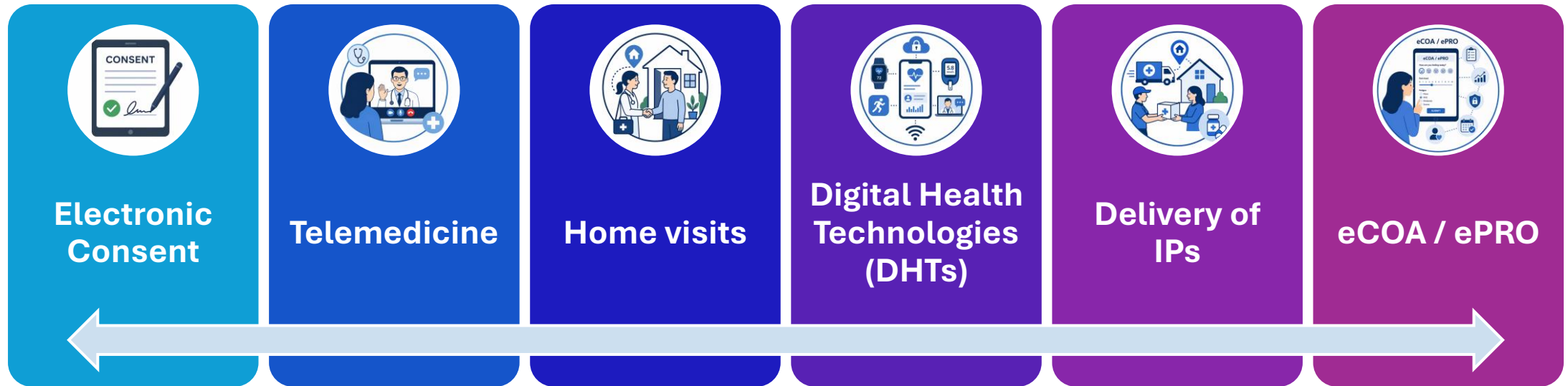
Pragmatic Elements



Real-World Data (RWD)

Decentralised Elements

- Trial-related activities conducted **outside the investigator's location** - for e.g., trial visits and/or protocol-related procedures conducted at the trial participant's home, local healthcare centres or mobile medical units.



IPs: Investigational Products

eCOA: electronic Clinical Outcome Assessments

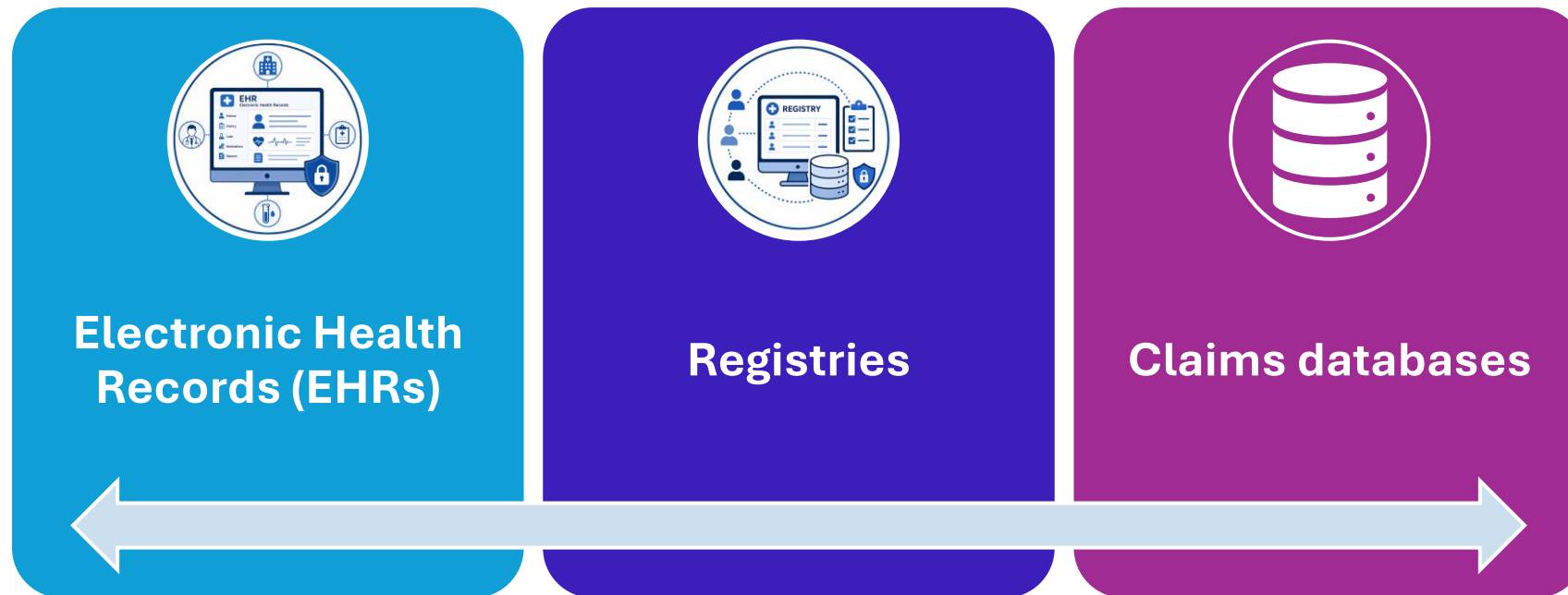
ePRO: electronic Patient Reported Outcomes

Pragmatic Elements

- 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.*
 - For example:
 - 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.
 - 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.

Real-World Data (RWD)

- RWD incorporated in interventional clinical trials refers to **use of data relating to patient health status** collected from a **variety of sources outside of clinical trials**.



Primary Data Collection vs Secondary Use of Data

In the context of clinical trials, data are often used in one of two ways as:



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.



Participant
in trial



Trial-specific
procedures



Data captured
prospectively

VS



SECONDARY USE OF DATA

- Refers to the use of data that were 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.

EXAMPLES OF DATA SOURCES



Clinical
assessments



Laboratory
tests



Imaging /
other tests



Participant
questionnaires

EXAMPLES OF DATA SOURCES (often RWD)



Electronic health
records (EHRs)



Registries



Claims
databases

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Communication with IRB/IEC

- When incorporating decentralised elements, pragmatic elements and/or RWD, particular attention should be given to:



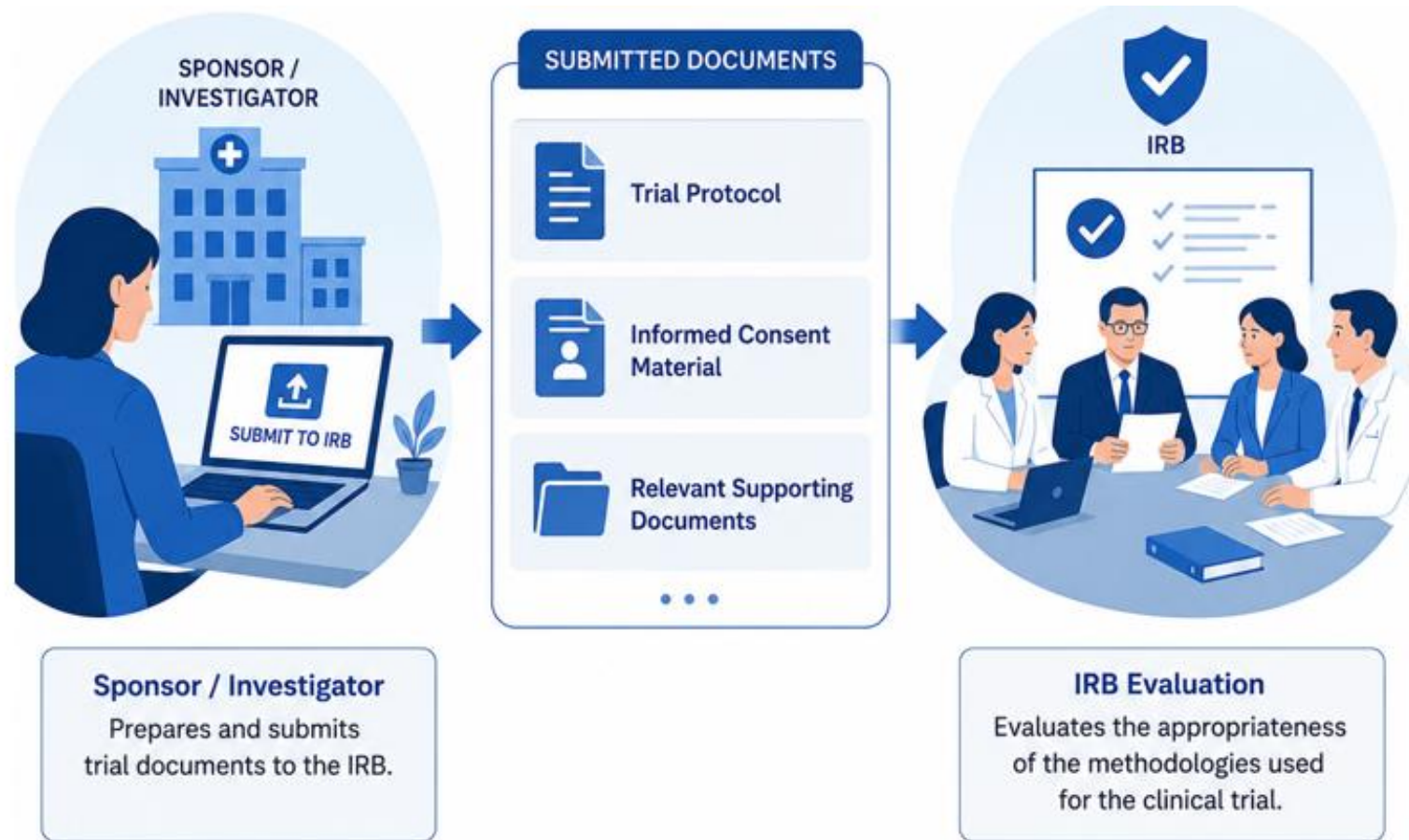
- Additional considerations may be required, for e.g., data protection.

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Communication with IRB/IEC

- Provide the IRB/IEC with the information needed for the **evaluation of the appropriateness of the methodologies being used.**



Informed Consent Considerations

- **Informed consent materials**

- **Tailored** to reflect the various **operational approaches, design elements** and **data sources** incorporated in the trial.
- Describe the:
 - Participant-related data to be collected;
 - Use of data in the trial; and/or
 - Parties who will have access to the participant's personal information (e.g., health records and home address).

- **Informed consent process**

- The **characteristics of the trial population** and the **appropriateness of the method and tools used to obtain informed consent** should be considered.
 - For e.g., When e-consent / remote consent is used, 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.

Informed Consent Considerations

- Remote consent

- Informed consent may be obtained remotely, where appropriate.
- The investigator should **assure themselves of the identity of the participant** (or legally acceptable representative, where applicable).
 - *For e.g., verification of a photo ID via a video call.*
 - *The verification method along with the measures to safeguard data privacy should be pre-specified.*

In-person Consent vs Remote Consent

In-person Consent



1 Verification of identity of participant



2 In-person discussion



3 Signing paper ICF or electronic ICF



4 Screening

Remote Consent



1 Verification of identity of participant



2 Virtual discussion



3 Signing paper ICF or electronic ICF by participant



4 Signing paper ICF or electronic ICF by investigator



5 Screening

IMPLEMENTING REMOTE CONSENT IN SINGAPORE



1



Consult the institution (e.g. IT department) on the acceptable telemedicine software to be used for remote consent.

5



Ensure that all parties sign and date the ICF.

2



- ✓ Secure connection
- ✓ Privacy protected
- ✓ Data integrity
- ✓ Confidentiality

Ensure that the informed consent discussion is conducted in a secure manner, and adequate measures are in place to safeguard participant privacy and data integrity and confidentiality.

6



Document details of the remote consent process in the participant's source records.

3



Provide a copy of the ICF (e-ICF/ hardcopy ICF) to the participant to read before the informed consent discussion.

4



Verify the identity of the participant during the remote consent discussion (e.g., by verifying a photo ID).

7



Retain the signed copy of the ICF (signed by all parties) at the investigator site in a manner that has secure and limited access and prevents unauthorised editing. The participant should also be provided a signed copy of the ICF in a similar manner.

Investigational Product (IP) Management

- Various **IP management approaches (supply, storage, dispensing, administration, return, accountability, destruction/alternative disposition)** may be utilised as appropriate.
- The IP may be **dispensed/supplied to the participant or appropriate designee** for administration at the participant's location (e.g., participant's home, local healthcare centre) by appropriate parties.
- All approaches should be arranged and conducted in accordance with applicable regulatory requirements.

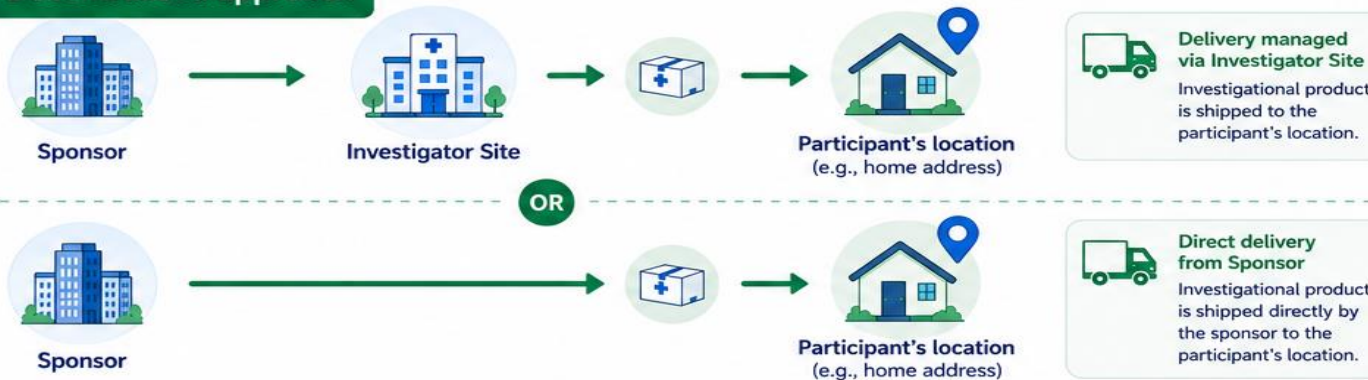
Direct to Participant Delivery of Investigational Products

i May be arranged by the investigator or sponsor.

1 Traditional approach



2 Decentralised approach



★ Important considerations

- ✓ Privacy / confidentiality (incl. disease status);
- ✓ IP will be received by intended recipient (e.g., participant, participant's legal representative or participant's caregiver);
- ✓ Process for IP receipt, storage, handling, administration, return, destruction / alternative disposition, accountability;
- ✓ Blinding protection (if applicable); and/or
- ✓ Availability of participant support tools



👥 In situations where the sponsor arranges for the DTP:



Investigator/institution **retains responsibility** for safe and appropriate investigational product use.



Investigator should be **aware of the arrangements** for shipping made by the sponsor.



Investigator remains **informed** of receipt, use, participant-reported issues, and resolution.



Roles/responsibilities of sponsor and investigator should be clearly documented.



Clear communication and **predefined procedures** required between sponsor, investigator, and any service provider, in accordance with applicable regulatory requirements.

Implementing DTP in Singapore

Key Considerations for Trial Sites



1



Provide written instructions to trial sites on handling and storage of the IP when using DTP services.

2



Inform trial participants about the DTP service and seek their consent to provide their contact details to the vendor.

3



Ensure that the trial participants' contact details are **not divulged** to the sponsor.

4



Ensure the IP is delivered to trial participants' homes within the recommended storage temperature for the IP and in a secured manner.

5



Consider viable **alternatives** in the event the trial participant / trial participant's legal representative is unable to receive the IP personally at home.

6



Provide written instructions to trial participants on using the IP, returning the used IP, and contact details of the investigator site staff for any enquiries. The investigators should ensure that trial participants use the delivered IP correctly in accordance with the protocol.

7



Ensure **traceability** throughout the IP supply chain.

8



Maintain documentation relating to shipment, receipt, storage, dispensing and accountability, return and destruction.

9



Ensure that trial participant privacy and data confidentiality are safeguarded.

10



Ensure that treatment blinding is not compromised by the DTP approach.

Alternative Approaches to IP Management in Singapore

- **For clinical trials of locally registered products regulated by HSA:**

IP Receipt

- IP Inventory Logs may not be required if the IP is supplied from pharmacy stock.
 - IP batch number and expiry date should be documented if this is not tracked by the pharmacy.

IP Storage

- Separate IP Storage Temperature Logs may not be required if the IP storage temperature is centrally monitored.
 - Alarm system required.

IP Preparation, Dispensing and Accountability

- IP preparation records may not be required if the IP is prepared per usual clinical practice.
- IP dispensing and accountability logs may not be required if there are other means to determine IP compliance (e.g., diary cards).
 - IP batch number and expiry date should be documented if this is not tracked by the pharmacy.

IP Return / Destruction

- IP destruction records may not be required if the IP is destroyed in accordance with the institutional policy.
 - Copy of SOP on destruction of pharmaceutical waste should be filed.

Investigational Product (IP) Management

- **Investigator oversight**

- Investigator oversight of IP receipt, use, return (or alternative disposition), commencement, continuation, dose and dose adjustments of the IP, as specified in the trial protocol.
- Investigator oversight level depends on trial design, IP characteristics, route and complexity of IP administration, existing safety knowledge of the IP, and marketing status of IP.

- For e.g.,

Open-label trials

Oral tablets

Locally registered products

Randomised, double-blind controlled trials

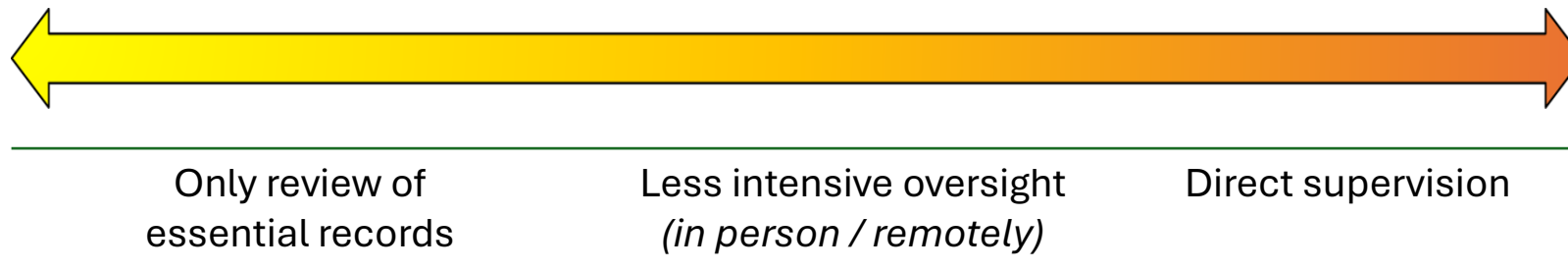
Injectables

Unregistered products



Investigator Oversight

- Maintain **proportionate** and **appropriate** oversight of trial-related activities.
 - Rights, safety and well-being of the trial participants; and
 - The reliability of the trial data.
- **Proportionate level of investigator oversight**
 - Importance of the data being collected; and
 - Risk to participant rights, safety and well-being, and data reliability.
- **Appropriate level of investigator oversight**
 - Context dependent (e.g., depending on trial characteristics, such as trial design, trial population, investigational product and data sources).

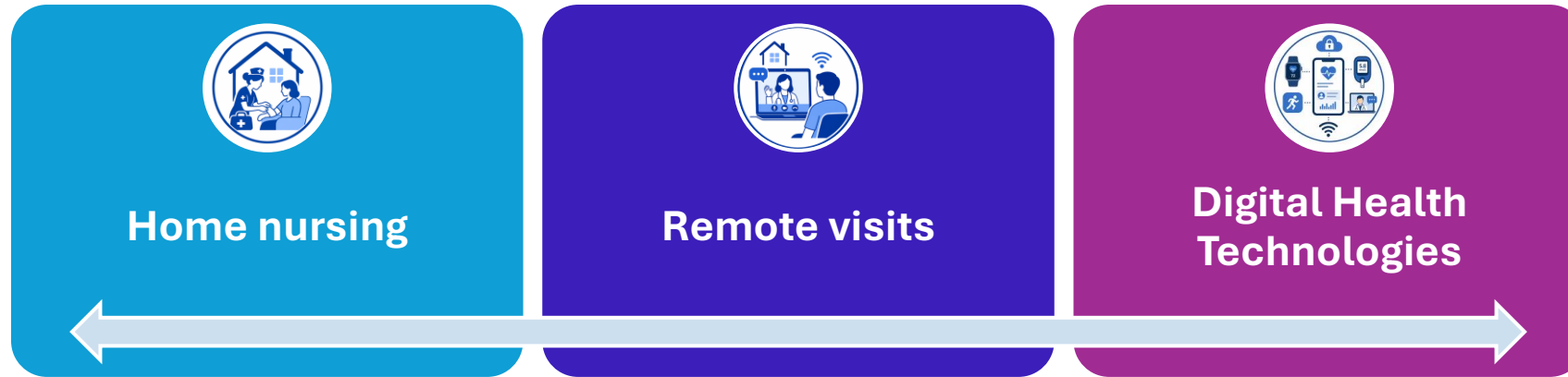


Investigator Oversight

- **Use of healthcare professionals to conduct trial-related activities within usual clinical practice**
 - Described in the protocol.
 - **For trial-related activities that are part of usual clinical practice and do not require knowledge about the trial protocol, investigator's brochure or other trial-related documents:**
 - Appropriate arrangements should be in place (e.g., agreements or documented arrangements).
 - Address plans for making relevant information and records on the performed trial-related activities available to the investigator (e.g., defining how data are shared, how records are retained, how data privacy is maintained and what mechanisms are in place for ensuring data integrity).
 - **For trial-related activities that are part of usual clinical practice and require knowledge about the trial protocol, investigator's brochure or other trial-related documents:**
 - Delegated healthcare professionals who have been appropriately trained should perform these activities.
- In any case, the **level of investigator oversight** should be **proportionate** to the **criticality of the data** to **participant protection and the reliability of the trial results**.

Safety Assessment and Reporting

- Safety information may be generated from various sources – e.g.,



- The investigator should **review and assess information** on the **health status of participants** across the sources of safety-related information.
- The **safety information** 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**.

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Engagement and Communication

Patients, patient advocacy groups and their communities

- Refine trial design
- Address logistical issues
- Determine training needs

Healthcare professionals and Investigators

- Determine infrastructure requirements
- Develop protocols to incorporate usual clinical practice of HCPs
- Determine training needs

Regulatory Authorities

- Discuss appropriateness of using such methodologies in the design of their trial
- Identify challenges and strategies for resolution

Early engagement ensures the successful integration and implementation of the methodologies used in trials.

Protocol and Trial Design

General requirements

- **Describe the design elements, data sources** and where appropriate, **various operational approaches** in the trial protocol, including their **rationale and justification** for the appropriateness of their use, **fitness for purpose and feasibility**.

Clinical trials incorporating pragmatic elements

- Assess for **fitness for purpose**.
- Ensure that the protocol clearly describes **how, by whom, and under what circumstances** these trial-related activities will be performed.

Clinical trials incorporating data from various data sources or practice settings

- Consider **the impact of data variability** in the **trial design**.
- Discuss the impact in the protocol or protocol-related documents (e.g., statistical analysis plan).

Protocol and Trial Design

Training and technical support

- Consider the **methodologies used in the clinical trial** when **determining the need for appropriate training and technical support** to be provided to the **investigator, investigator site staff and participants**.

Safety Information

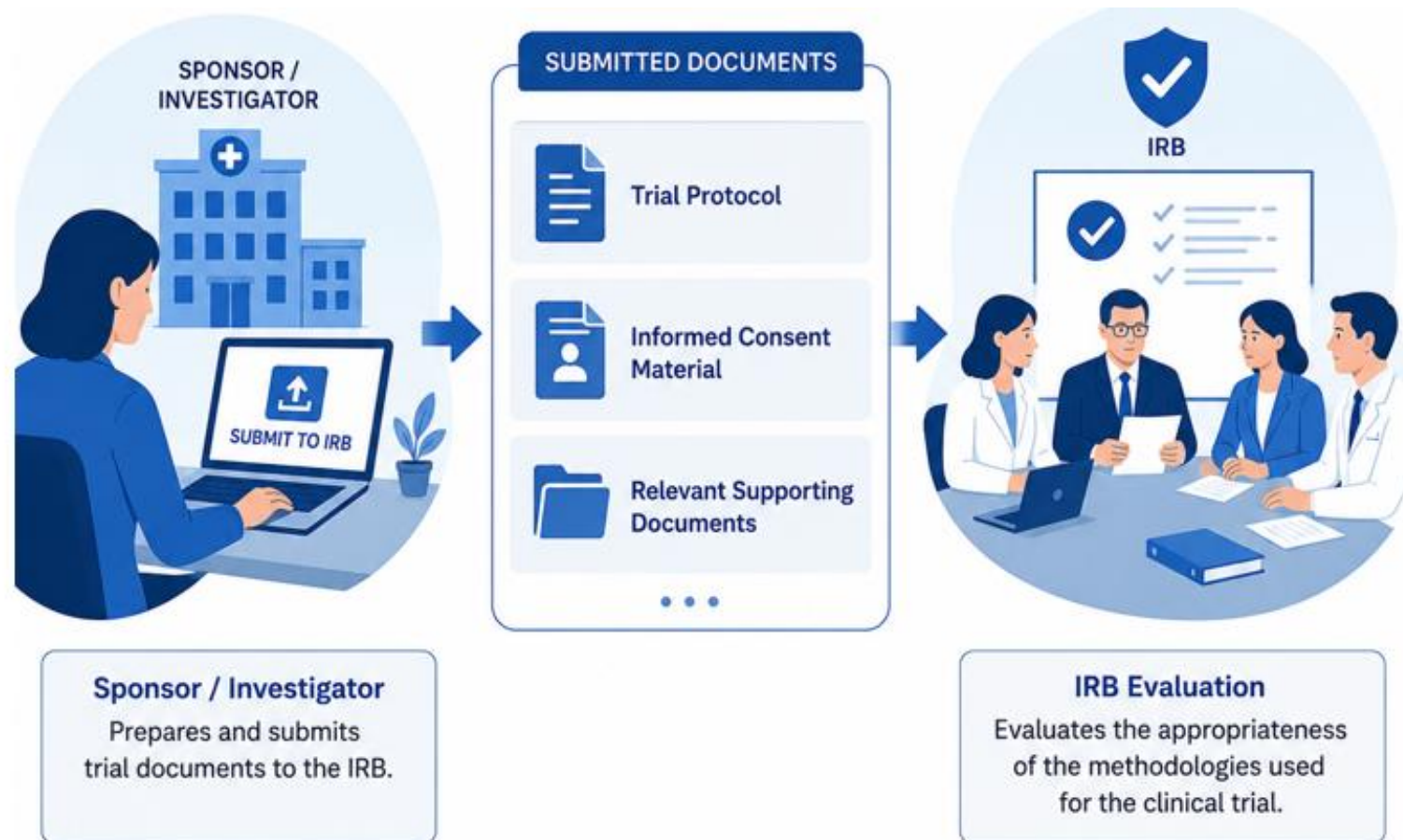
- Describe:
 - **How safety information will be collected from various data sources;**
 - **How data and information suggesting a potential safety concern will be identified and made available to the investigator in a timely manner;** and
 - **What actions should be taken by the investigators** in these instances.

Informed consent

- Describe the **modalities for informed consent process** (e.g., in-person / remote consent).

Communication with IRB/IEC

- Provide information needed for the **evaluation of the appropriateness** of the methodologies being used.



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Access to and Use of RWD

- RWD used in a clinical trial should be managed in a manner that **ensures participant protection** and the **reliability of trial results**.
- This includes ensuring that:



The RWD are **fit for purpose**.



Appropriate access and **oversight** are in place.



The use of RWD complies with applicable **privacy and data protection requirements**, including **consent and permission**.

Access to RWD

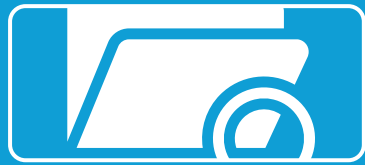
- RWD used in clinical trials may be derived from **individual-level data** or **data in source records**.

 Individual-level data	 Data in source records
 Datasets / listings capturing data for each individual, usually extracted from source records and structured for statistical analysis and reporting.	 Data in original records, such as patient medical records, laboratory reports, imaging files and physician notes, from which individual-level data are derived.
 Pseudonymised for trial use (i.e., a specific individual cannot be identified without collating the data with additional information).	 Typically, not pseudonymised (i.e., contains patient-identifying information and other information subject to data privacy and protection requirements).

- Sponsors should have **ability to access individual level data** and **data in source records** (as necessary in accordance with applicable regulatory requirements), for example, **to implement quality assurance and quality control activities**.
- Regulatory authorities** may require **access to individual-level data** and **data in source records** for regulatory inspections.

Access to RWD

- If RWD used in a clinical trial are owned and controlled by entities other than the sponsor (e.g., healthcare institutions, registry holders, insurers):
 - **Appropriate arrangements**



To **access** and **use** the data for **trial purposes**.



Allow the **sponsor** to **access source records** for **quality assurance and quality control**, as required by regulations.



Allow **Regulatory Authorities** to **access individual-level data and source records** for **regulatory inspections**.



Documented agreements should define **how data are shared and protected**, in line with regulatory requirements and institutional policies.

Access to RWD

- **Access to individual-level data and data in source records** should be **proportionate** to the **criticality of the data**.

For RWD use cases of higher criticality (e.g., key efficacy and safety endpoints)	For RWD use cases of lower criticality (e.g., for exploratory endpoints)
• Simply assessing the fitness for purpose of the RWD source to be utilised may be insufficient. • Sponsors may need to for example, 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, sponsors should consult relevant regulatory authorities.	• 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 or undertakes data processing steps, sponsors remain responsible for:**
 - Maintaining oversight of these steps, including extraction, linkage and transformation; and
 - Implementing quality assurance and quality control measures to ensure data are of appropriate quality.

Consent and Permission Considerations for RWD



- **Permission or approval** should be 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 (as applicable per regulatory requirements).



- The **informed consent material** should describe use of and access to RWD and source records by:
 - Regulatory authorities;
 - Sponsor representatives (where applicable); and/or
 - IRBs/IECs (where applicable)



- Such consent **does not imply** involvement 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),**
 - 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.



- The **records** of consent / permissions should be retained and made available to regulatory authorities upon request.

Data Considerations

- Should be read in conjunction with Annex 1, section 3.16.1 and section 4.

- **RWD Considerations**

- Ensure that the **RWD is fit for purpose**, based on their:

Reliability	Relevance
▪ Includes accuracy, completeness, provenance and traceability.	• 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 paid to the **variability in the data source, potential bias, generalisability and traceability of RWD.**

Data Considerations

- In selecting RWD sources:

Assess

- Whether the data are appropriate to support the specific trial objectives and endpoints.

Weigh

- The potential benefits against limitations, taking into account the considerations from the fitness for purpose assessment.

Reflect

- These considerations in trial planning, protocol design and oversight processes.

- Fitness for purpose assessment of RWD source

- **Assess whether the RWD source is fit for purpose for the intended use of the trial.**
 - 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**.

Data Considerations

Considerations for Fitness for Purpose assessment for RWD sources



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



Lack of standardised timing of data collection and procedures.



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.



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).



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.



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



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.

Data Considerations

- **RWD Considerations**

- **When data are linked from multiple sources to support reliability, including completeness of RWD, ensure:**
 - Data to be linked are **pre-specified in the protocol and protocol-related documents**, including how data inconsistencies between different sources will be resolved in a systematic and consistent manner;
 - **Accurate matching to the individual** is **assured**; and
 - **Adequate measures** to sufficiently **protect both data privacy** and the **reliability of trial results**.
- **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**.

Data Considerations

- **Remote Data Collection Considerations**

- Remote data collection in clinical trials requires special attention to be paid to **data security vulnerabilities**, including **cybersecurity and data privacy**.
- Some of the RWD considerations may also apply to remote data collection.

Investigational Product (IP) Management

- **Assess approaches to IP management during protocol development, considering:**



IP stability, including any specialised storage conditions



IP preparation and route of administration



Trial population



Knowledge about the safety profile of the IP



Need for in-person clinical observation post-IP administration



**Need for emergency plans related to IP administration
(e.g., requirement for rescue medication)**



Measures needed to protect blinding, if applicable.

Investigational Product (IP) Management

- **Direct to Participant (DTP) delivery of IPs**
 - **Sponsor may arrange to send the IP to the participant** (e.g., to the participant's home) in accordance with applicable regulatory requirements:

Protocol compliance

- **IP shipment** should be carried out in accordance with the **protocol**.

PI Authorisation

- **IP shipment process** may **only be initiated** after being **authorised by the investigator**.

Safeguards

- **Trial participant privacy** and **confidentiality** are taken into consideration.

- Sponsor may **deploy systems** (e.g., IRT or DHTs) and **assist investigators to establish the processes** (e.g., home visits) to ensure that the allocated IP was delivered to trial participants and administered appropriately.

Privacy and Confidentiality Considerations

- **Security safeguards**, including cybersecurity, should be in place to **protect the privacy and confidentiality of personal information of participants**.
- **Participants' personal information:**
 - May be **required by service providers**, for example, for IP shipment to participants or deployment of home nurses.
 - **Access** should be **limited to those authorised**.
 - **Appropriate informed consent** is required from the participants.
 - **Risk of potential disclosure of personal information from a data breach** (e.g., data from DHTs and/or RWD) should be considered.

Sponsor Oversight

- Sponsor oversight should ensure 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**.
 - This includes:

Processes

- Ensuring there are **processes in place**, including **clear lines of communication**.

Quality Assurance and Quality Control Measures

- Implementing **quality control and quality assurance measures** specifically customised to the clinical trial and its critical to quality factors and identified risks, with these measures being implemented in a **risk-proportionate manner**.

Oversight of service providers

- Ensuring **appropriate oversight of service providers**, including **maintenance of their essential records**.

Sponsor Oversight

- **When the sponsor arranges trial-related activities under the responsibility of the investigator, for example, home nursing.**

Sponsor

- Ensure that **service providers are suitable** to conduct the trial-related activity.

Investigator

- **Retains the final decision to decide on the appropriateness of the proposed service provider; and**
- **Maintains oversight of the trial-related activities.**

Note:

This requirement intends to cover trial-related activities under the responsibility of the investigator involving interaction (e.g., face to face, telephone, email) with the participants (such as home nursing). It is generally not intended to cover trial-related activities undertaken centrally by a sponsor-arranged service provider that do not involve interaction with participants (such as biological sample analysis by a central laboratory).

Safety Assessment and Reporting

- **Safety information**

- **Management of safety information** is essential to **protect trial participants' safety** through **early detection** and **management of potential adverse drug reactions**.
- May be **collected in various ways** and **from multiple sources** in clinical trials with **decentralised and/or pragmatic elements**.
 - Appropriate processes and procedures should be in place to make the safety information accessible to the investigator in a timely manner, according to the protocol.
 - 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.
- **Approach to safety management** (including mitigating actions to safeguard participant safety) and reporting should:
 - Be described in the protocol or protocol-related documents (e.g., safety management plan).
 - Consider the methodologies used in the trial.

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Summary

- Annex 2 provides additional considerations for interventional clinical trials that incorporate:
 - Decentralised elements;
 - Pragmatic elements; and/or
 - Real-World Data
- The appropriate and proportionate application of GCP will support these approaches, while safeguarding participants' rights, safety and well-being, and helping to ensure the reliability of trial results.

Implementation Timelines for ICH E6 (R3) GCP guideline in Singapore



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References

- [ICH E6 \(R3\) GCP Guideline](#) [*consolidated guideline for Principles, Annex 1 and Annex 2*]
- [ICH Step 4 slide deck on Annex 2 of ICH E6 \(R3\) GCP Guideline](#)
- [HSA Regulatory Guidances](#)
 - [Electronic Consent](#)
 - [Alternative Approaches for Investigational Product Management for clinical trials of locally registered products](#)
 - [Conduct of Clinical Trials in relation to the COVID-19 situation](#)

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