Investigator-Initiated Studies: When you’re the Sponsor

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Session Objectives

- Define roles of the investigator, sponsor and sponsor-investigator.

- Describe the actions required to meet the obligations of being a sponsor during all stages of a research project.

- Outline considerations for multi-centre trials and the use of Contract Research Organizations (CROs).
ICH GCP Role Definitions

Investigator

• A person responsible for the conduct of the clinical trial at a trial site.

• If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator (PI).
ICH GCP Role Definitions

**Sponsor**

• An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.
ICH GCP Role Definitions

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 subject.

• The term does not include any person other than an individual (e.g., it 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.

ICH E6 5.1
What does it mean when you’re the sponsor-investigator?

Roles of the Investigator

• Protecting the rights, safety and welfare of subjects in the clinical study
• Ensuring that informed consent is properly obtained from clinical trial subjects
• Conducting the clinical study (that is, directly overseeing the administration of the test products to the subject). In situations where there is a team of researchers, the investigator will act as the team leader
• Ensuring that the clinical trial is conducted in accordance with the signed agreement and the investigational plan
• Controlling the products under investigation (for example, supervising medical-device use and disposal)
• Ensuring proper record-keeping and reporting requirements are met (for example, mandatory safety reporting)

Roles of the Sponsor

• Selecting the investigator(s)
• Providing investigator(s) with the necessary information to conduct the clinical trial
• Ensuring proper monitoring of the clinical study
• Ensuring all the necessary ethic review(s) and approval(s) are obtained
• Preparing and submitting clinical trial application(s) and amendment(s) to the appropriate regulatory agencies
• Ensuring that any reviewing ethics board and regulatory agencies are promptly informed of any significant new information in a clinical study
• Ensuring compliance with labeling, reporting and record-keeping requirements
• Ensuring that the clinical study is conducted in accordance with Good Clinical Practice (GCP)
PDCA

Plan → Do → Check → Act (Adjust) → Plan

Deming Circle – Shewhart Cycle
PDCA

Plan

Act (Adjust)

Check

Do
ICH GCP Section 5 outlines Sponsor Responsibilities, during set-up the sponsor-investigator must consider:

- Section 5.1 – Quality Assurance & Quality Control
- Section 5.3 – Medical Expertise
- Section 5.4 – Trial Design
- Section 5.5 – Trial Management, Data Handling, & Record Keeping
- Section 5.7 – Allocation of Responsibilities
- Section 5.8 – Compensation to Subjects and Investigators
- Section 5.9 – Financing
- Section 5.10 – Notification/Submission to Regulatory Authorities
- Section 5.11 – Confirmation of Review by IRB
- Section 5.12 – Information on Investigational Product
You’ve got a great idea, now what?

- **Medical Expertise** (5.3)
  - Who else do you need on your team to ensure you gather the right information to get an answer to your question?

- **Trial Design** (5.4)
  - How do you structure the trial to ensure that the answer you get really is the right answer?

- **Financing** (5.9)
  - How do you pay for the study to make sure that you get the answer?
  - What kind of costs might you incur for the procedures necessary? (Section 5.8)

ICH E6 Sections 5.3; 5.4; 5.9 (with a little Section 5.8)
Setting up for Success

• **Trial Management, Data Handling, & Record Keeping (5.5)**
  – Doing this well makes it easier to continually appraise the data collected, make changes where necessary and answer the study question.

• **Allocation of Responsibilities (5.7)**
  – Identify who you need on your team and engage them from the start – they will help you identify potential pitfalls of the trial and ways to work around them.
Setting up for Success (cont.)

• Compensation of Subjects and Investigators (5.8)
  – Who is ultimately taking responsibility for the trial, including necessary insurance and financial coverage against claims arising from the trial?

• Information on Investigational Product (5.12)
  – What product are you using? How are you getting it? This needs to be identified before proceeding with regulatory applications.

ICH E6 5.5; Section 5.7; 5.8 (the rest of it); 5.12
Quality Assurance and Quality Control

- The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs.
- Quality control should be applied to each stage of data handling.
Quality Assurance & Quality Control

All those *planned and systemic actions that are established* to ensure that the trial is performed and data are generated, documented (recorded), and reported in compliance with GCP and other regulatory authorities [ICH1.46]

Examples:
- SOPs
- Worksheets / checklists / templates
- Training records

The operational techniques and activities undertaken within the quality assurance system to *verify that the requirements for quality related trial-related activities are fulfilled* [ICH1.47]

Examples:
- Source Document Verification
- Informed Consent Process Followed
- Review of Regulatory Binder
Monitor & Auditing – complement each other

The act of **overseeing the progress of a clinical trial**, and ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP and applicable regulatory requirement(s) [ICH 1.38]

- QC function
- Site - study conduct is routinely assessed on an ongoing basis at every step of the trial
- Required per ICH GCP (Health Canada)

A **systematic and independent examination** of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor’s SOPs, GCP and other applicable regulatory requirements [ICH1.6]

- Top-down systematic evaluation of trial processes and QC
- Site’s and sponsor’s processes
- Not continuously done, rather snapshots
- Not required per ICH GCP
Monitoring

• Sponsor should ensure that the trial is adequately monitored

• The purposes of trial monitoring are to verify that:
  – The rights and well-being of human subjects are protected
  – The reported trial data are accurate, complete, and verifiable from source documents
  – The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s)
Monitoring Plan (cont.)

• Who is responsible for oversight? Is a DSMB needed?
• What will be monitored?
• When will monitoring occur?
• Who will be doing the monitoring?
• What will be reported? And to whom?
• What is the process for responding to recommendations?
Monitoring Plan (cont.)

• Extent and natural of monitoring considers:
  – Objective, purpose, design, complexity, blinding, size, and endpoints of the trial
  – FDA: additionally, clinical status of participants, site experience, amount of study data
  – Other: trends

• Types of monitoring:
  – Central, Onsite or Remote
  – SDV: Targeted or Risk-based
  – Adaptive monitoring
  – Hybrid
Monitoring (cont.)

• Sponsor appoints the monitors
  – Selection and Qualification of Monitors
  – Monitor’s Responsibilities - see 5.18.4

• Monitoring Procedures
  – Sponsor’s written SOPs and trial-specific

• Monitoring Report
  – Written report after each visit

ICH E6 5.18
Monitoring - References

Auditing

- The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

- Selection and Qualification of Auditors

- Auditing Procedures

ICH E6 5.18
Getting the Approvals

- **Notification/Submission to Regulatory Authorities (5.10)**
  - Health Canada CTA: Do you need one?
  - Which division do you need to submit to?

- **Confirmation of Review by REB (5.11)**
  - Submission to Health Canada and the REB must be identical; if one or the other asks for changes the same changes must be made to both applications.

ICH E6 5.10, 5.11
PDCA

Plan

Do

Check

Act (Adjust)
Do - Study Initiation and Ongoing Management

• Before you can manage the trial as the site investigator you need to set up the processes for ongoing trial management:
  – Section 5.13 – Manufacturing, Packaging, Labeling, and Coding Investigational Product
  – Section 5.14 – Supplying and Handling Investigational Product
  – Section 5.15 – Record Access
  – Section 5.16 – Safety Information
  – Section 5.17 – Adverse Drug Reaction Reporting
Investigational Product

• In the planning stage you identified what products you were going to use but you also need to identify how you are going to use them.

• Regulatory Agencies are going to be looking closely at how you source and manage the IP so having written procedures for this is of the utmost importance.

ICH E6 5.13, 5.14
Record Access

• When you are the sponsor-investigator record access is a simpler task as you have access to all of the source documentation.

• With that said, you need to ensure that you have the correct approvals in place with your local team to ensure that if there is an audit by an outside agency (i.e. Health Canada) they have access to the same documentation you used to create your study dataset.
Safety Reporting

- **Adverse Drug Reaction Reporting (5.17)**
  - As the sponsor-investigator you are responsible for submission of ADR to the regulatory authority and the REB who approved the trial
  - Creating a process for this will ensure that all ADRs are reported according to the regulatory guidelines applicable for your trial

- **Safety Information (5.16)**
  - The sponsor is responsible for the ongoing safety evaluation – as the sponsor-investigator you may consider forming a Data Safety Monitoring Board to assist with the evaluation of safety

ICH E6 5.16, 5.17
Monitoring Plan in Action

• Who is responsible for oversight? Is a DSMB needed?

• What will be monitored?

• When will monitoring occur?

• Who will be doing the monitoring?

• What will be reported? And to whom?

• What is the process for responding to recommendations?
Quality Control

- **Site**
  - PI has adequate qualifications, resources
  - Staff - training, functions
  - Following approved protocol and all approved amendments, SOPs

- **Participants**
  - Written consent
  - Eligible participants

- **Investigational Product(s)**
  - Manufacturing, Packaging, Labelling, and Coding
  - Supplying and Handling

- **Safety Information**
  - ongoing safety evaluation and notification

- **Adverse Drug Reaction Reporting** – REB, reg. authorities
  - serious and unexpected

- **Completeness of data**

ICH E6 5.13-5.17
PDCA

Plan

Check

Do

Act (Adjust)
Clinical Trial/Study Reports

The sponsor should ensure:

• that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s)

• also that the clinical trial reports in marketing applications meet the standards of the ICH Guidance for Structure and Content of Clinical Study Reports.

ICH E6 5.22
Making the adjustments

• In “Check” you’ve discovered what elements of the trial might be improved, now you need to look back and see how you can change your “Plan” to make those improvements.

• Some improvements might involve changes to the protocol or participant safety and these will require amendment submissions to Regulatory Body and REB.

• See the Health Canada Guidance Document for Clinical Trial Sponsors – What is an amendment and what is a notification?
Noncompliance

- With the protocol, SOPs, GCP, and/or applicable regulatory requirement(s)
- Sponsor is to take prompt action to secure compliance
- Corrective action can include:
  - Amendment to the protocol
  - Training of staff, creating a SOP
Noncompliance (cont.)

• Serious and/or persistent noncompliance on the part of an investigator/institution, sponsor should
  – terminate the investigator's / institution's participation in the trial
  – notify promptly the regulatory authority(ies)
Other Considerations

- Multicentre trials
- CRO
Multicentre Trials

• Investigator Selection
• Strict compliance with the protocol
• CRFs
• Responsibilities documented prior to start of the trial
• Facilitate communication
Multicentre Trials - Agreements

• Including:
  – Financial
  – Data access
  – Material Transfer

• From all involved parties and in writing, as part of the protocol or in a separate agreement
Contract Research Organization (CRO)

• A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO and should be specified in writing

• Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor

• The ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor

ICH E6 5.2
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