

Investigator Responsibilities and Good Clinical Practice (GCP)

ICH E6 Good Clinical Practice Guidance

Disclaimer

- ▶ Note that this is a general slide presentation designed for a broad audience of clinical researchers.
- ▶ Accordingly, some sections may not apply to your protocol.
- ▶ Information that may not be applicable for all studies is indicated via *blue italics*.

Disclaimer (continued)

- ▶ Examples include references to:
 - *Investigational Product (IP), the Investigator's Brochure (IB), or a study pharmacist*
 - *Safety reporting and adverse events*
 - *Randomisation and unblinding procedures*
 - *Regulatory authorities*
 - *Clinical treatment (for a behavioral or study or a registry)*

Information that may be helpful but does not come directly from ICH is identified by this icon.



Basis for Research Roles and Responsibilities: Guidelines & Regulations

- ▶ Good Clinical Practice (GCP) Guidelines (ICH-E6)
 - Widely accepted international research standards
- ▶ EU Clinical Trials Directives
 - Directives of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

What is GCP? ICH 1.24

- ▶ A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials [studies],
- ▶ that provides assurance that the data and reported results are credible and accurate,
- ▶ and that the rights, integrity, and confidentiality of study subjects are protected.



Why is GCP Important?

- ▶ Sets minimum quality standards for the conduct of clinical research
- ▶ Compliance with GCP
 - Ensures that the rights, safety, and well-being of study participants are protected
 - Ensures the integrity of the data submitted for approval
- ▶ Sets standards for a system of mutual accountability among sponsors, regulatory authorities, investigators, and IRBs

Realm of GCP in Critical Care Studies

- ▶ The regulations and guidelines concerning the establishment of good clinical practice apply to all studies involving human subjects
- ▶ Applies to
 - Interventional studies, including studies without an investigational product
 - Observational studies (specimen collection studies, natural history, etc.)
 - Device studies

PI Commitments: Investigator Qualifications and Agreements ICH 4.1

- ▶ Properly qualified to assume responsibility for conduct of the study
- ▶ *Thoroughly familiar with the investigational product (IP), and its appropriate use*
- ▶ Willing to comply with GCP and applicable regulations and be prepared for audits and monitoring
- ▶ Maintain a Delegation of Responsibilities log

PI Commitments: Adequacy of Resources ICH 4.2

- ▶ Ability to recruit in sufficient numbers and on time
- ▶ Sufficient time to complete the study
- ▶ Adequate number of qualified staff and adequate facilities to complete the study
- ▶ Staff who are well informed about the protocol, *the IP*, and their study responsibilities

PI Commitments: Medical Care of Trial Participants ICH 4.3

- ▶ Ensure that all trial-related medical decisions are made by an investigator who is a qualified physician
- ▶ *Provide adequate medical care for participants who experience adverse events*
- ▶ Notify the participant's primary physician of his/her participation (as appropriate)
- ▶ Make an effort to learn why participants withdraw

PI Commitments: Communication with the IRB/IEC ICH 4.4

- ▶ Obtain written approval before the study begins
- ▶ *Provide the IRB with the current Investigator's Brochure*
- ▶ Provide the IRB/IEC with all documents subject to its review throughout the trial

PI Commitments: Compliance with the Protocol ICH 4.5

- ▶ Conduct the trial in compliance with the protocol
- ▶ Deviate only with agreement from the sponsor and prior review/approval from the IRB/IEC
There can be exceptions – see next slide!
- ▶ Document and explain all deviations

PI Commitments: Compliance with the Protocol ICH 4.5

- ▶ The investigator may deviate from the protocol before obtaining agreement from the sponsor and review/approval from the IRB/IEC **only**:
 - When the changes are logistical/administrative, or
 - To eliminate an immediate hazard to study subjects. This requires immediate submission to:
 - the IRB
 - the sponsor
 - regulatory authorities (if required)

PI Commitments: Investigational Products (IP) ICH 4.6

- ▶ *Responsible for the product, its usage, and its storage*
- ▶ *May delegate to a Pharmacist under the PI's supervision*
- ▶ *Maintain IP records*
- ▶ *Store as specified by the sponsor and in accordance with applicable regulatory requirement(s)*
- ▶ *Use IP in accordance with the protocol*

PI Commitments: Randomisation and Unblinding Procedures ICH 4.7

- ▶ *Follow the study randomisation procedures*
- ▶ *Ensure that the randomisation code is only broken in accordance with the protocol*
- ▶ *Promptly document and notify the sponsor of any unblinding (for blinded trials)*


PI Commitments: Informed Consent ICH 4.8

- ▶ Adhere to GCP and the ethical principles that have their origin in the Declaration of Helsinki
- ▶ Update consent document when new information becomes available
- ▶ Avoid:
 - Coercion or undue influence
 - Language that causes the participant to waive any legal rights

PI Commitments: Informed Consent ICH 4.8

ICH 4.8


- ▶ Fully inform participant of all pertinent aspects of the trial
- ▶ Use lay and non-technical language
- ▶ Should be understandable to the subject

 Translated to native language as applicable (IRB must approve translations)

- ▶ Provide enough time for participant to review the consent document and ask questions

PI Commitments: Informed Consent ICH 4.8

ICH 4.8

- ▶ The consent document must be signed and dated
 -  Obtain consent prior to start of any study-related activities. Initial phone screening can precede consenting.
- ▶ If a participant or representative is unable to read, a witness should be present during the consenting process
- ▶ Provide the participant with a copy of the signed and dated consent form

PI Commitments: Informed Consent

ICH 4.8

- ▶ The informed consent discussion and the consent document should include all essential and additional elements
- ▶ Essential elements include:
 - Statement that the study involves research
 - Statement that participation is voluntary
 - Information about purpose, duration, and procedures

PI Commitments: Informed Consent

ICH 4.8

- ▶ Essential elements (continued):
 - Number of subjects involved in the study
 - Description of risks, benefits, and alternatives
 - Information about compensation/care for injury
 - Statement regarding confidentiality of records
 - Description of possible unforeseen risks

PI Commitments: Informed Consent

ICH 4.8

- ▶ Essential elements (continued):
 - Circumstances for termination without subject consent
 - Consequences of withdrawing from the study
 - Additional costs that may result from participation
 - Statement that new research findings will be shared
 - Contact information for questions/concerns

PI Commitments: Records and Reports

- ▶ ICH 4.9 (Records and Reports)
- ▶ ICH 4.10 (Progress Reports)

PI Commitments: Records and Reports

ICH 4.9

- ▶ Data must be ALCOA (Accurate, Legible, Contemporaneous, Original, and Atttributable) and complete
 - How and where the data is recorded is key!
 - If it is not documented, it does not exist
- ▶ Data on CRFs should match the source documents (raw data)

PI Commitments: Records and Reports

ICH 4.9

- ▶ All changes to a CRF must be dated and signed such that the original data is not obscured
- ▶ Retain essential documents for at least 2 years after the last approval of a marketing application
- ▶ Provide monitors, auditors, IRB/IEC, *or regulatory authorities* with direct access to trial records



Records and Reports

- ▶ Record SAE events thoroughly
 - Meets criteria
 - PI to determine causality
 - Follow-up information
- ▶ Make records available to monitors, auditors and inspectors
- ▶ Record retention
 - Institutional requirements
 - ICH GCP – 2 years after last approval of marketing application in an ICH region
 - Follow protocol, NIH, and local institutional requirements
 - Longest requirement should be followed



Records and Reports

- ▶ Essential Documents
 - Permit evaluation of the conduct of the study and the validity of the data
 - ICH GCP E6 section 8.0 provides a table of essential documents, the purpose of the document, and the location broken down according to the stage of the study
 - Approved documents maintained at centralized location with copies (protocol) at satellite locations
 - Reviewed for completeness and accuracy



Records and Reports

- ▶ Essential Documents (Examples)
 - CVs for PI and Sub-Investigators
 - Training records for all study personnel
 - Protocol / amendment signature page
 - IRB approvals – of protocol, consents, ads, handouts
 - Communication – with IRB, sponsor, CRO, if applicable

PI Commitments: Progress Reports to Sponsor/IRB/IEC

ICH 4.10

- ▶ Submit a written report at least annually and in accordance with the IRB's request
- ▶ Submit a written report if there are changes that might significantly change the conduct of the trial and/or increase risk to subjects

PI Commitments: Safety and Safety Reporting

- ▶ ICH 4.11 (Safety Reporting)
- ▶ ICH 4.12 (Premature Termination or Suspension of a Trial)

PI Commitments: Safety Reporting

ICH 4.11

- ▶ *Immediately report all SAEs to the sponsor; follow-up with a written report*
 - EXCEPTION: SAEs identified in protocol as not requiring immediate reporting*
- ▶ *Identify study participants using codes rather than personal identifiers*
- ▶ *Comply with applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC*

PI Commitments: Safety Reporting

ICH 4.11

- ▶ Report AEs and/or lab abnormalities critical to safety evaluations to the sponsor per protocol
- ▶ Provide the sponsor and IRB with additional requested information
 - Autopsy report in the event of a death
 - EKG or other supporting documentation

PI Commitments: Premature Termination or Suspension of a Study

ICH 4.12

Condition	Notify
Study terminated/suspended	All participants
PI terminates study	Institution, sponsor, IRB*
Sponsor terminates study	Institution, IRB*
IRB terminates study	Institution, sponsor*

* Notify in writing

PI Commitments: Final Report(s)

ICH 4.13

- ▶ At study completion, the investigator should provide:

Documentation	Provided to
Notification of study completion	Institution*
Summary of the trial's outcome	IRB/IEC
Any required report(s)	Regulatory Authority(ies)

*Where applicable



Examples of Common Non-Compliance

- ▶ Insufficient evidence of Investigator involvement/oversight
- ▶ No documented delegation of responsibility/scope of work
- ▶ Failure to adhere to protocol requirements
- ▶ Inadequate source documents
- ▶ Changes made to original records without audit trail of when, why, by whom
- ▶ Failure to report SAEs appropriately
- ▶ Participants not signing most current version of consent form
- ▶ *Inadequate product accountability records*



Consequences of Non-Compliance

- ▶ Non-compliance runs the gamut from simple mistakes to fraud.
- ▶ Even simple mistakes can be costly!
 - Consent
 - Specimen handling and processing (labeling, etc.)
- ▶ Consequences can range from:
 - Loss of data (Subject, Site, or Study data considered invalid)
 - Professional/reputational risk for PI and institution



Applying GCP to Your Study

- ▶ Understanding is key to protecting subject safety and integrity of data
- ▶ Monitoring and quality management help ensure compliance
- ▶ Ultimately, it is the PI's responsibility

Resources

- ▶ ICH E6 Guideline
 - <http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html>

Resources

Objective	Resource
Staff qualifications/training	ICH E6, Sec 4.1, Sec 4.2
Research resources	ICH E6, Sec 4.2
Protocol adherence	ICH E6, Sec 4.5
Record keeping	ICH E6, Sec 4.4.1, Sec 4.9, Sec 8

Questions?