ICH-GCP
An Overview of Investigator’s Responsibilities

International Committee on Harmonization
Good Clinical Practice

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What is ICH?

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

GOAL: Harmonization of Technical Requirements for product registration in three regions (US, EU, Japan) to reduce or obviate the need for duplicate the R&D testing by region

MEMBERSHIP: Regulatory Agencies from US, EU and J and pharmaceutical industry experts (US = PhRMA)

HOW: Stepwise approach to recommending and endorsing harmonized requirements (FDA publishes guidances in Federal Register)
ICH-GCP Definition and Purpose

ICH-GCP guidelines are an international ethical and scientific quality standard which have their origins in the Declaration of Helsinki, for all clinical trials that involve the participation of human subjects.

The rights, safety and well-being of the subjects are the most important considerations.

ICH GCP was adopted by FDA in May 1997 as the accepted standard for conducting clinical trials for registration.

Strict adherence to ICH-GCP guidelines ensures that these considerations are met and that the quality of the research can be assured.
ICH-GCP Definition and Purpose

Addressed within the guidelines are sections defining:

Responsibilities for

- the EC/IRB
- the Investigator
- the Sponsor

Requirements

- of a protocol
- for an Investigator’s Brochure
- for documentation

The focus of this presentation is Responsibilities of the Investigator
Who can be an Investigator?

An investigator ....

- is a **qualified physician** who is responsible for all trial-related medical decisions

- must have suitable **education, training** and **experience** in the field being researched and also have a knowledge of **GCP** and applicable regulatory requirements

- may **delegate some of their responsibilities** to other individuals. This delegation must be documented and these individuals must also be suitably educated and trained to perform the role and have a knowledge of GCP.

*Prior to starting the study, the Investigator must provide an up to date, signed and dated Curriculum Vitae (CV) to confirm points 1 and 2 above. A CV may also be requested by the EC/IRB and/or the Regulatory Authorities*
An Investigator must have the time and availability to perform the study, this includes:

- regular meetings with the study monitor
- identification and screening of subjects
- longer/more frequent contact with subjects than standard practice
- completion of the paperwork including source data and entering data into the Case Record Form (electronic or paper)
- meetings with auditors, inspectors and external suppliers (as applicable)
- meetings with other study staff to review the progress of the trial
What are some of the Investigator’s responsibilities?

- Study Protocol
- Study Personnel
- Study Equipment
- EC/IRB Involvement
- Subject Recruitment
- Subject Informed Consent
- Recording Data
- Source Documents
- Product Accountability
- Safety Reporting
- Records and Reports
Responsibilities: Study Protocol

The investigator MUST:

know and adhere to:

- Protocol and any subsequent amendments
- Investigator’s Drug Brochure
- Product information

formally agree to comply with the protocol and confirm this by signing the protocol

not deviate from the protocol without prior agreement from the Sponsor

not implement protocol amendments prior to review and approval by EC/IRB and Regulatory Authorities

- **EXCEPT** to remove immediate hazard from the subject

*Any deviations from the protocol must be documented and explained*
Responsibilities: Study Personnel

The Investigator must ensure

There are adequate numbers of qualified site staff to conduct all aspects of the trial

All site staff involved with the study are adequately informed and trained on the

- Protocol
- Investigational product
- Their delegated tasks & duties

Ongoing maintenance of a document listing appropriately qualified persons to whom significant study-related duties have been delegated
Adequate facilities and equipment must be available for the duration of the study.

All equipment must comply with protocol requirements, used appropriately and have maintenance records, e.g. calibration records, servicing history.

Sponsor may provide some of the required study equipment and this must be used in accordance with the instructions for use.
Responsibilities: EC/IRB Involvement (1)

Investigator / Institution must have written Ethics Committee approval before the initiation of the trial: The documents submitted for approval include:

- Protocol, Consent Form, written information provided to the subjects, Investigators Brochure, Investigator Qualification
- Recruitment methods, e.g., poster or advertisement

During the study, if new information becomes available requiring changes in the trial, the new version of the documents previously submitted (e.g. Protocol Amendments, New Informed Consent Form ...) must be submitted and approval obtained from EC/IRB prior to their implementation, UNLESS immediate action is needed to maintain subject safety.

Any revision of the documents previously submitted that occurs during the trial must be made available to the EC/IRB.
Responsibilities: EC/IRB Involvement (2)

Written summaries of the trial status should be submitted to the EC/IRB annually (or more frequently if required by EC/IRB) and they should be notified of study completion.

Specific national and local Ethics Committee/IRB requirements or regulations should be followed.
Responsibilities: Subject Recruitment

The Investigator must

Demonstrate a potential for recruiting the required number of suitable subjects within the agreed timeframe (e.g. from an analysis of retrospective data) and provide this to the Sponsor. Remember entry criteria may exclude subjects and some subjects will not want to participate.

→ Be realistic in your predictions

Keep a log for screened and recruited subjects

Take time to review data and follow inclusion and exclusion criteria

→ Discuss with the Sponsor if you have questions regarding the inclusion/exclusion of a subject or are experiencing problems finding suitable subjects
Responsibilities: Informed consent (1)

Prior to any study related procedures being performed (unless also a part of routine care), the subject must have freely given his/her consent. The Investigator or the person designated by the Investigator must obtain the informed consent of the study subjects. The subject and the person obtaining the informed consent must personally sign and date the Informed Consent Form.

If new important information becomes available during the study it may be required for the subjects to be given additional information and sign a new consent form. The same process as for initial consent should be followed.
Responsibilities: Informed consent (2)

Subjects should be:

- fully informed about the trial verbally and in writing in a language/style understandable to them

- given reasonable time to ask questions and to decide whether or not participate in the study

- Given a copy of the consent form
Responsibilities: Informed consent (3)

Special procedures exist for subjects considered
- vulnerable,
- unable to give consent e.g. in emergency situations.

Such procedures will be detailed in the protocol and EC/IRBs/Regulatory Authorities may have specific requirements that must also be followed.

If a legally acceptable representative is required to sign the informed consent on the subject’s behalf, as soon as/if the subject subsequently recovers enough to be informed, the Investigator must ensure the informed consent process is followed and consent obtained from the subject.
The data reported to the sponsor must be:

- accurate
- complete
- legible
- completed in a **timely** manner

Data reported in the CRF must be consistent with the data in the source documents.

Any corrections to data recorded in the CRF must not obscure the original entry and must be initialed and dated and a reason for the change given if not obvious. Electronic CRFs must have an audit trail.

*The permissible clarification process enables monitors to make certain clarifications to the CRF, following written agreement by the Investigator at the start of the study.*
Source document: Source documents are original documents, data, and records or copies/transcriptions certified after verification as being accurate copies. Examples of such documents include but are not limited to:

- subject notes, hospital records or charts
- laboratory reports
- subject diaries
- pharmacy dispensing records
- x-rays / CT scans / MRIs
- recorded data from automated instruments
- microfilm or magnetic media

It should be possible to reconstruct the data in the CRFs from data recorded in the source documents
General guidance for good documentation practices

- All documents should clearly identify the subject to whom they relate
- Records should be consistently organised
- Records should be bound to prevent loss
- Person making the entry should be clearly identified
- Any copies of originals must be certified/confirmed as true copies if they are to become the source
- Use of loose sheets of paper is discouraged and if used they should be attached to permanent records to prevent loss
- Recording of data in more than one place is discouraged e.g. first in a notebook and then in the subject’s chart
Monitors / Auditors / Inspectors check source documents and CRFs to

- ensure entries in the CRF/eCRF are consistent with source data recorded in subject files and that any inconsistencies are corrected or explained
- ensure the source documents are adequate and accurate

*Best practice: The Monitor and the Investigator agree on the minimum data to be recorded in the source documents and identification and location of source for each data item at the start of the study and on an ongoing basis.*
Responsibilities: Product Accountability

Investigator / Institution is responsible for accountability of study medication. The investigator may delegate this task to an appropriately qualified person (i.e. Pharmacist)

The following detailed records for study medication must be maintained, including dates and amounts

- confirmation of receipt from the sponsor
- dispensed and returned medication for each subject
- medication returned to the sponsor/destroyed

No medication (dispensed or returned) can be destroyed or disposed of without prior agreement with the sponsor

Instructions related to storage conditions must be followed and documented

*Take time to explain to each subject how to take the study medication and remind the subject to return the empty/unused treatment packs to ensure and measure compliance*
All adverse events must be recorded in the CRF and source documents.

All AEs classed as Serious must, within **24 hours** of awareness, be reported to the sponsor. The events must also be reported to the EC/IRB.

The initial report of a SAE should be followed promptly and detailed, written follow-up must be reported to the sponsor.

The Investigator must supply the sponsor and EC/IRB with any additional information requested e.g. autopsy reports, discharge letters.

In cases of notification of expedited safety reports to Health Authorities for serious and unexpected events (7/15 day IND Safety Reports), the investigator is responsible for reporting the events to their ethics committees.
If it is **NOT** documented **it does not exist**

- Sites are responsible for archiving study related documents (Investigator Site File, CRFs, source data) for the period of time discussed with the monitor. However, at any time prior to destroying any of the above records, the Investigator must inform the sponsor to confirm if it is acceptable for records to be destroyed or if other arrangements need to be made.
- The Investigator should inform Sponsor in the event of relocation or transfer of archiving responsibilities.
- All local regulations and laws regarding archiving requirements must be adhered to.
- Written summaries of the trial status should be submitted to the EC/IRB annually (or more frequently if required) and at trial conclusion.
What are some of the Sponsor Responsibilities?

- Implement and Maintain QA and QC systems
- Secure agreements in writing on all elements of trial execution
- Trial Quality and Integrity
- Designate appropriately qualified medical personnel for trial related medical questions
- Utilize qualified individuals for all stages of the trial process
- Selection of Qualified Investigators
- Subject Insurance (as applicable)
- Notification/Submission to Regulatory Authority (ies)
- Confirmation of IRB/IEC Review
- Appropriate background work on IP
- Manufacturing, Packaging, Labeling, Coding, Supplying and Handling IP
- Ongoing Safety Evaluation and Reporting
- Monitoring and Auditing
- Addressing Noncompliance
- Reporting Results
Monitor’s Responsibilities

The purpose of monitoring is 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/amendments, with ICH-GCP and with the applicable regulatory requirements
Monitor’s Responsibilities (2)

The Monitors

Act as the main line of communication between the sponsor and the Investigator

Verify the investigational product availability and storage, correct use and records

Verify that the Investigator follows the approved protocol/amendments

Verify that written informed consent was obtained before each subject participation in the trial

Ensure that the Investigator and all trial staff have all the information required to conduct the trial

Verify that the Investigator is enrolling only eligible subjects
The Monitors

Perform Source Document Verification by comparing the data recorded in the source documents to the data entered in the CRFs/eCRFs

Inform the Investigator of any CRF entry error and ensure necessary corrections are made

Determine whether all adverse events are appropriately recorded and reported

Determine whether the Investigator is maintaining all the essential documents

Communicate deviations from the protocol, standard operating procedures or ICH-GCP to the sponsor
What is an Audit?

A systematic and independent examination of trial related activities and documents to determine if these activities were

- recorded
- analyzed
- accurately reported

according to the

- protocol
- Standard Operating Procedures
- GCP
- applicable regulatory requirements
How are sites selected for audit?

Site selected for an audit based on

- Contribution to the Study(ies)
- Geographical Location
- Random selection
- Pre-Health Authority Inspection
- Problems identified or Complaints
What does an Investigator site audit involve?

Introductory Meeting to explain the aims and conduct of the audit
Interviews with Study Personnel assessing study conduct
Review of:
  - facilities (tour)
  - investigator documentation on site and at Sponsor (or External Supplier)
  - data (for example)
    - source documents including patient notes
    - consent forms
    - drug accountability
    - transcription into CRF/EDC
Close-out meeting to discuss the main points, and answer/resolve any outstanding questions
Follow Up to Address issues identified
Regulatory Authority(ies) Inspections
What is an inspection?

The act by a Regulatory Authority(ies) of conducting an official review of

- documents
- facilities
- records
- and many other resources

that are deemed by the Authority(ies) to be related to a clinical trial and that may be located

- at the site of the trial
- at the sponsor’s and/or contract research organization’s (CRO’s) facilities
- or at other establishment(s) deemed appropriate by the Regulatory Authority(ies)
What is the purpose of a Site Inspection?

The overall aim of Regulatory Authorities is to:

- ensure the protection of human subjects
- ensure the quality and integrity of data
- enforce compliance with regulations

At FDA, the Division of Scientific Investigations (DSI) is responsible for Bioresearch Monitoring Program (BiMO) Inspections. These include site inspections for GLP, BE and GCP for Investigators, Sponsor-Monitors, CROs and IRBs.
Inspections vary both in timing and performance depending on Regulatory Authority:

- following submission of a marketing application
- following notification of a clinical trial
- as a routine inspection of facilities
- for cause (complaints)
- with or without notification
- single inspector or a team of inspectors
- sponsor and investigator site or investigator site alone
- inspections by foreign Regulatory Authority (e.g., FDA inspection at EU investigative site)
FDA Classification of Inspections

**Routine**
- Inspections assigned for IND’s and NDA’s

**Directed ("for cause")**
- Problems identified during review process
- Complaints reported to DSI
  - FDA, other Agencies
  - Sponsors/monitors
  - Institutions/IRB’s
  - Subjects/Public
When Does FDA Perform Bioresearch Monitoring Inspections?

- Clinical Investigator inspections are performed for nearly every new NDA/PLA/PMA relying on “pivotal” clinical trial data for demonstration of efficacy and safety.
- Clinical trials supporting important efficacy supplements may also be subject to Bioresearch Monitoring (BiMo) inspections.
- Phase IV studies are subject to routine BiMo inspections.
- Clinical studies of any phase or stage of completion may be inspected if there exist data integrity concerns.
Site Selections: “Who & Why”

Importance of the study
- Relevance to labeling/NDA
- Contribution/size/outliers

Statistical impact of data from the site

History of the clinical investigator
- Frequency and classification/findings of previous inspection(s)
Clinical Investigator Inspections
Center for Drug Evaluation & Research
FY 97-02

Source: FDA Presentation at SQA 16JUL03
Clinical Investigator Inspections
Center for Drug Evaluation and Research - FY 2002
(Domestic and International)

60%
33%
7%

Source: FDA Presentation at SQA 16JUL03
CI “For Cause” Inspection Assignments
(CDER, FY’s 92-02)

Source: FDA Presentation at SQA 16JUL03
Clinical Investigator Deficiency Categories*
CDER Inspections - FY 01

*Foreign & Domestic

Source: FDA Presentation at SQA 16JUL03

n=285
Misconduct and Fraud in Clinical Research

Scientific misconduct can be defined as:

“…execution of a study in a way that compromises the validity or reliability of the findings, or violation of the rights of individuals who participate in the study”

Shapiro, Charrow: Scientific misconduct in investigational drug trials, NEJM 312 (1985): 731

Misconduct differs from non-compliance in that it compromises the study and/or violates the subject’s rights

Fraud is only a small aspect of misconduct and includes the intent to deceive.
Examples of Misconduct excluding Fraud

Honest error or honest differences of opinion

- Failure to obtain approval for a protocol, or changes to a protocol, from IRB/Regulatory Authority
- Revealing confidential information about a subject(s)
- Persistent of significant deviation from the protocol
- Failure to report adverse events
- Failure to obtain informed consent
What Makes one Suspicious?
A few examples

Lack of availability of investigator, rescheduling visits, empty waiting rooms, only available off hours

Consistency in handwriting / writing instrument / markings across patient or source documents

Notations in patients notes squeezed in between lines

Altered source data to aid inclusion of patients

Data collected at the beginning used through-out the study

Photocopied charts

Medication packaging consistently stressed or opened in the same way

Similar trends in drug supply

“Too compliant”