Good Clinical Practice (GCP): the Investigational Products and Investigator's Responsibilities

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Disclaimer

Note that this is a general slide presentation designed for a broad audience of clinical researchers.

Accordingly, some sections may not may not be applicable for all studies.

Acknowledgements

The presentation is based on Good Clinical Practice (GCP) Guidelines (ICH-E6) and widely accepted international research standards

Some of the slides are taken from CROMS Clinical Research Operations and Management Support website

Who is involved with GCP?

- Sponsor - An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial (1.53, ICH GCP 2016)
- Investigator – A person responsible for the conduct of the clinical trial at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator (1.34, ICH GCP 2016)
- Sub investigator – Any individual member of the clinical team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (eg. associates, residents, research fellows). 1.56, ICH GCP 2016)

Reasons for GCP Training

- The right, safety, and wellbeing of human subjects are protected
- Clinical Trials are conducted in accordance with approved plans with integrity
- Data obtained from clinical trials are reliable

ICH Guideline for GCP E6 (R1)

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

GUIDELINE FOR GOOD CLINICAL PRACTICE
E6(R1)

Current *Step 4* version
dated 10 June 1996

(including the Post Step 4 corrections)

In this presentation:

- Investigator's Qualification and Agreements ICH 4.1
- Adequate Resources ICH 4.2
- Medical Care of Trial Participants ICH 4.3
- Communication with the IRB/IEC ICH 4.4
- Compliance with the Protocol ICH 4.5
- Investigational Products (IP) ICH 4.6
- Randomization and Unblinding Procedures ICH 4.7
- Informed Consent ICH 4.8
- Records and Reports ICH 4.9
- Progress Reports ICH 4.10
- Safety Reporting ICH 4.11
- Premature Termination or Suspension of a Study ICH 4.12

GCP: Difference between Clinical Research and Standard Care

- Involves human volunteers, these may be patients or can be healthy individuals who are not suffering from an illness or condition
- Testing an intervention or collecting data through interviews or observations
- Measures effects over a period of time using robust and reliable methods
- Is carried out with the ultimate aim of improving standard care

GCP: Difference between Clinical Research and Standard Care

- Will study issues such as improved care, better treatments or therapies, additional support, costs etc.
- May involve a comparison "control" group
- Focuses on unknowns such as the effect of intervention, the likelihood of a community to change their practices, etc.
- May stick to a protocol without deviation.
- Standard care is all about clinical judgment, decision, decision making and flexibility

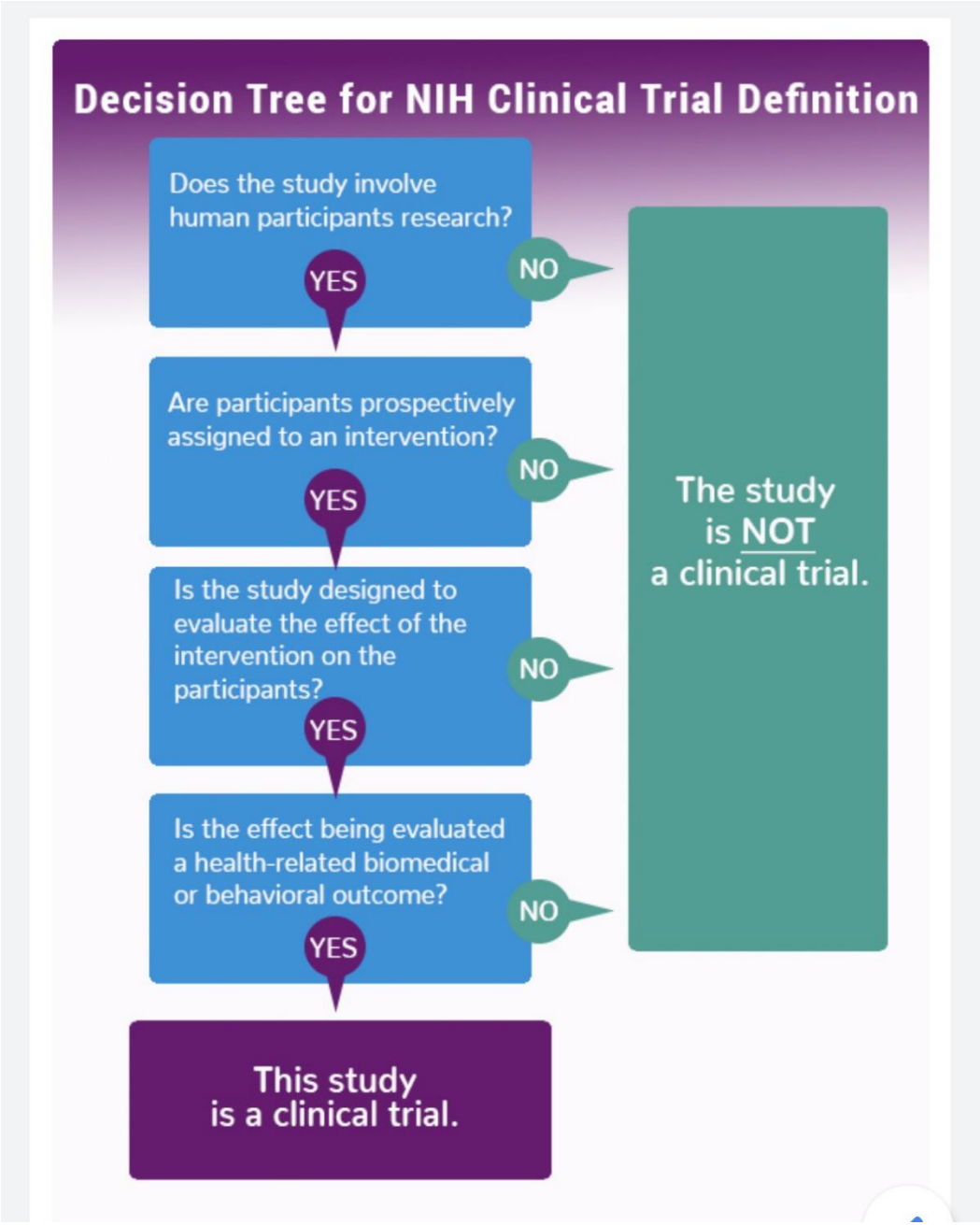
Clinical Trial and Clinical Study

Q1. Are the subjects prospectively assigned to an intervention (potential drug/ medical device/ activity/ procedure)? – Interventional Clinical Study

Q2. Is the study designed to observe participants on their current treatment plan and track health outcomes – Observational Clinical Study

What is a Clinical Trial? NIH

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.
(Oct 23, 2014)


Decision Tree for NIH Clinical Trial Definition
Does the study involve human participants research?
YES
NO
Are participants prospectively assigned to an intervention?
YES
NO
Is the study designed to evaluate the effect of the intervention on the participants?
YES
NO
Is the effect being evaluated a health-related biomedical or behavioral outcome?
YES
NO
The study is NOT a clinical trial.
This study is a clinical trial.

NIH definition of a Clinical Trial?

Q1. Does the study involve human participants?

Q2. Are the subjects prospectively assigned to an intervention (potential drug/ medical device/ activity/ procedure)?

Q3. Is the study designed to evaluate the effects of the intervention?

Q4. Is the effect being evaluated as health-related biomedical or behavioral outcomes ?

Who runs a clinical trial? - Investigator

- Each clinical trial team is led by a physician
- The clinical trial team includes doctors and nurses as well as pharmacists and other health care professionals.
- The clinical trial team is responsible for checking the health of the participants at the beginning of the trial, monitoring them during the trial, and staying in touch with them for a period of time after the clinical trial has been completed.

HHS: Investigator

Investigator Responsibilities FAQs

Do the human research regulations apply to non-U.S. institutions? +

Who are "investigators"? −

The HHS regulations at 45 CFR part 46 use the term "investigator" to refer to an individual performing various tasks related to the conduct of human subjects research activities, such as obtaining informed consent from subjects, interacting with subjects, and communicating with the IRB. For the purposes of the HHS regulations, OHRP interprets an "investigator" to be any individual who is involved in conducting human subjects research studies. Such involvement would include:

HHS: Investigator

- Obtaining information about living individuals by intervening or interacting with the for research purposes;
- Obtaining identifiable private information about living individuals for research purposes;
- Obtaining the voluntary consent of individuals to be subjects in research and
- Studying, interpreting, or analyzing identifiable private information or data for research purposes

PI Commitments: Investigator's Qualification and Agreements ICH 4.1

- ✓ Investigator(s) should be qualified by education, training, and by CVs
- ✓ Investigator(s) should be familiar with investigational product(s)
- ✓ Investigator(s) should be aware of, and should comply with GCP and applicable regulatory requirements
- ✓ Investigator/Institution should permit monitoring and auditing by the sponsor

PI Commitments: Adequate 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 investigational product(s) 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 agreed by the sponsor and IRB/IEC
- Deviate only with agreement from the sponsor and prior review/approval from the IRB/IEC
- Document and explain all deviations

PI Commitments: Compliance with the Protocol ICH 4.5 contd

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 Investigational Product (IP) records

Store as specified by the sponsor and in accordance with applicable regulatory requirement(s)

Use IP in accordance with the protocol

Investigational Products
Therapeutic goods

1. Medicine

- Products that act by pharmacological, chemical, immunological, or metabolic means in or on the body of human
- (includes biological medicines e.g. monoclonal antibodies, vaccines - plasma derivatives, recombinant products)

Investigational Products Therapeutic goods

2. Medical Devices

- Any instrument, apparatus, appliance, material or other article intended to be used for human beings for the purpose of one or more of the following:
  - Diagnosis, prevention, monitoring, treatment or alleviation of disease,
  - Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,

Investigational Products Therapeutic goods

Medical Devices

- Investigation, replacement or modification of the anatomy or of a physiological process
- Control of conception
- OR an accessory to such an instrument, apparatus, appliance, material or other article

Investigational Products Therapeutic goods

3. Biological

- Product made from, or that contains, human cells or human tissues or organs and that is used to :
  - Treat or prevent disease, ailment, defect or injury,
  - Diagnosis a condition of a person,
  - Alter a physiological process of a person,
  - Test the susceptibility of a person to disease,
  - Replace or modify a person's body parts

Investigational Products Therapeutic goods

4. Other therapeutic good

- Product that is not regulated specially as a medicine, biological or medical device
  - (includes disinfectants, tampons)

Investigational Product

- Approved by FDA or like-wise agency
- Special authorization +/-
- Safety Records from previous studies
- GMP of the producer

PI Commitments: Randomization and Unblinding Procedures ICH 4.7

- Follow the study randomization procedures
- Ensure that the randomization code is only broken in accordance with the protocol
- Promptly document and notify the sponsor of any unblinding (for blinded trials: accidental unblinding, unblinding due to a serious event)

PI Commitments: Informed Consent 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

  8th grade reading level

  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 contd

- 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
  - Number of subjects involved in the study

PI Commitments: Informed Consent
ICH 4.8 contd

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: Informed Consent
ICH 4.8 contd

- Explain the study to the extent it can be understood by participants who can only be enrolled with the consent of a legally acceptable representative (LAR)
- Follow guidelines for nontherapeutic trials (trials in which there is no anticipated direct clinical benefit to the participant)
- If participant and LAR can't provide consent, follow measures described in the protocol

PI Commitments: Records and Reports
ICH 4.9

- Data must be ALCOA
  - (Accurate, Legible, Contemporaneous, Original, and Attributable) and complete
  - How and where the data is recorded
  - 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

PI Commitments: Records and Reports
ICH 4.9

Record UP/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

PI Commitments: Records and Reports
ICH 4.9

- **Essential Documents**

  Permit evaluation of the conduct of the study and the validity of the data

  Approved documents maintained at centralized location with copies (protocol, MOP) at satellite locations

  Reviewed for completeness and accuracy

PI Commitments: Records and Reports ICH 4.9

Essential Documents (Examples)

CVs for PI and Sub-Investigators

Licenses, as appropriate

Training records for all study personnel

Protocol / amendment signature page

IRB membership list or roster

IRB approvals – of protocol, consents, ads, handouts

Communication – with IRB, sponsor, CRO, if applicable

PI Commitments: Progress Reports
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 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: Premature Termination or Suspension of a Study
ICH 4.12

Condition	Notify
Study Terminated/Suspended	All participants
PI Terminates study	Institutions, sponsor, IRB*
Sponsor Terminates study	Institutions, IRB*
IRB Terminates study	Institutions, 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	RIB/ERC
Any required report(s)	Regulatory Authority(ies)

** Where applicable*

Resources

Electronic Code of Federal Regulations

http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&tpl=%2Findex.tpl

Office for Human Research Protections (OHRP)

http://www.hhs.gov/ohrp/

ICH E6 Guideline

http://www.ich.org/fileadmin/Public-Web-Site/ICH Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_Guideline.pdf

ICH http://www.ich.org/home.html

ICH GCP E6 Consolidated Guidance

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/ucm073122.pdf

Times up!!!
Thank you for your attention!!!