Learning Objectives:

- History
- GCP and FDA Regulations
- GCP Principles
- Investigator Responsibilities

Background

Nuremberg Doctors Trial 1946-1947

Declaration of Helsinki 1964

Background

The 1970s and 1980s

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)

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

What is GCP?

An international ethical and scientific quality standard for designing, conducting, performing, monitoring , auditing, recording, analyzing and reporting trials that involve the participation of human subjects

Compliance with standard

- provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki,
- and that clinical trial data are credible

OHRP
Office for Human Research Protections

Common Rule 45 CFR 46
Subpart A: Basic HHS Policy for Protection of Human Research Subjects

- IRB
- IRB review of research
- Informed Consent

FDA U.S. FOOD & DRUG ADMINISTRATION

21 CFR 50 Protection of Human Subjects • Informed Consent	21 CFR 312 IND
21 CFR 56 IRB	21 CFR 812 IDE
	21 CFR 11 Electronic records; electronic signatures

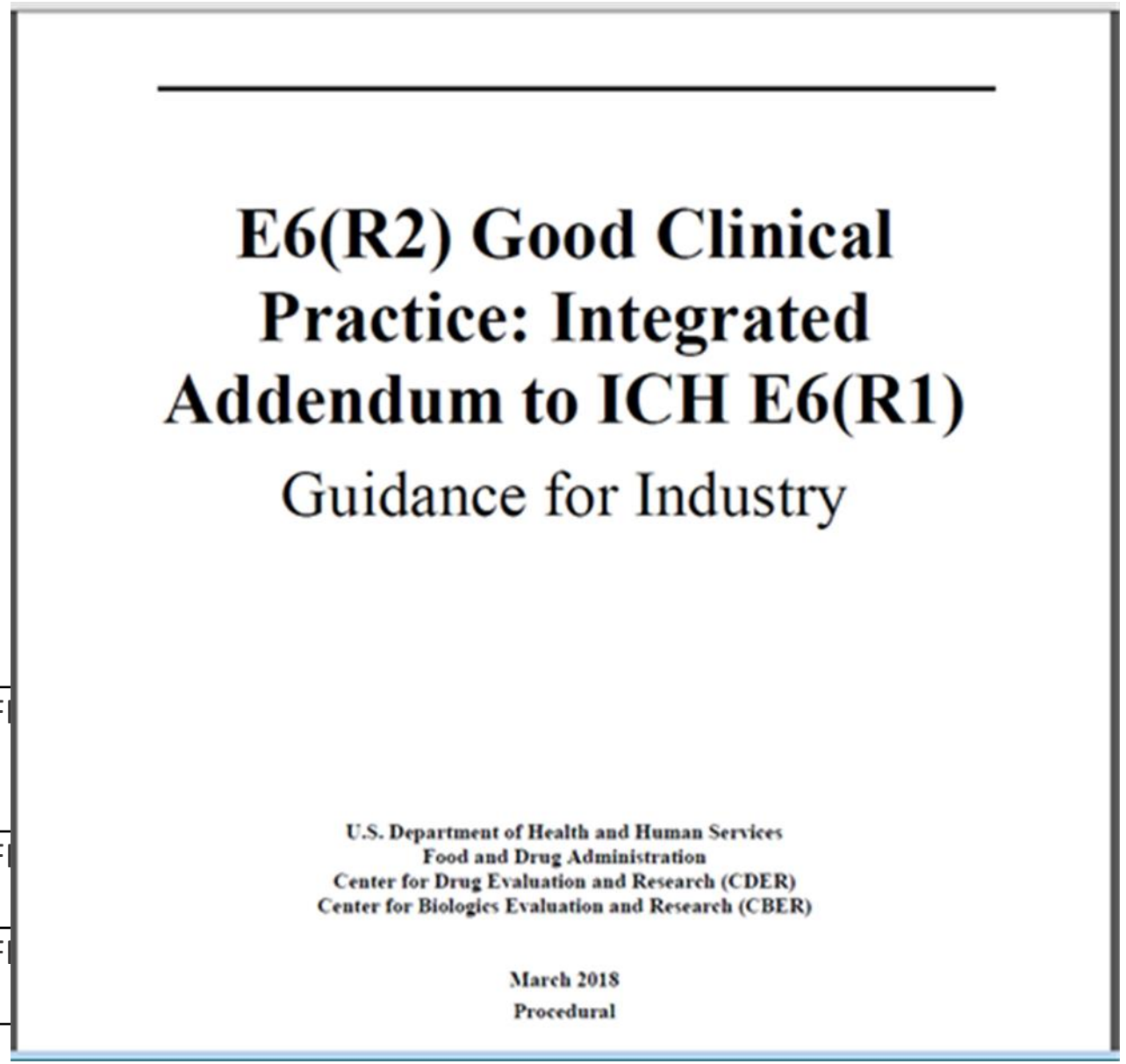
ICH
harmonisation for better health

Addendum to ICH
E6 (R2)

Some, but not all…

FDA U.S. FOOD & ADMINISTRATION

21 CFR 50 Protection of Human Subjects • Informed Consent	21 CF
21 CFR 56 IRB	21 CF
	21 CF



E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2018
Procedural

13 Principles

for the conduct of clinical research

- Ethics
- Protocol and Science
- Responsibilities
- Informed Consent
- Data Quality and Integrity
- Investigational Products
- Quality Control/Quality Assurance

13 Principles

Ethics

Protocol and Science

Responsibilities

Informed Consent

Data Quality and Integrity

Investigational Products

Quality Control/Quality Assurance

- Ethical conduct of clinical trials
- Benefits justify risks
- Rights, safety, and well-being of subjects prevail

13 Principles

Ethics

Protocol and Science

Responsibilities

Informed Consent

Data Quality and Integrity

Investigational Products

Quality Control/Quality Assurance

- **Nonclinical and clinical information supports the trial**
- **Compliance with a scientifically sound, detailed protocol**

13 Principles

Ethics

Protocol and Science

Responsibilities

Informed Consent

Data Quality and Integrity

Investigational Products

Quality Control/Quality Assurance

- IRB/IEC approval prior to initiation
- Medical care/decisions by qualified physician
- Each individual is qualified (education, training, experience) to perform his/her tasks

13 Principles

Ethics

Protocol and Science

Responsibilities

Informed Consent

Data Quality and Integrity

Investigational Products

Quality Control/Quality Assurance

- **Freely given from every subject prior to participation**

13 Principles

Ethics

Protocol and Science

Responsibilities

Informed Consent

Data Quality and Integrity

Investigational Products

Quality Control/Quality Assurance

- **Accurate reporting, interpretation, and verification**
- **Protects confidentiality of records**

13 Principles

Ethics

Protocol and Science

Responsibilities

Informed Consent

Data Quality and Integrity

Investigational Products

Quality Control/Quality Assurance

- **Conform to GMP's and used per protocol**

13 Principles

Ethics

Protocol and Science

Responsibilities

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Investigational Products

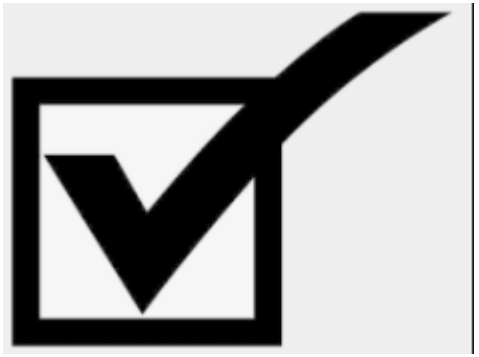
Quality Control/Quality Assurance

- **Systems with procedures to ensure quality of every aspect of the trial**

Application of GCP

True or False: FDA regulations include all parts of ICH GCP.

- True
- False



Investigator Responsibilities

(4.1) Investigator Qualifications and Agreements

(4.2) Adequate Resources

(4.3) Medical Care of Trial Subjects

(4.4) Communication with IRB/IEC

(4.5) Compliance with Protocol

(4.6) Investigational Products

(4.7) Randomization Procedures and Unblinding

(4.8) Informed Consent of Trial subjects

(4.9) Records and Reports

(4.10) Progress Reports

(4.11) Safety Reporting

(4.12) Premature Termination or Suspension of Trial

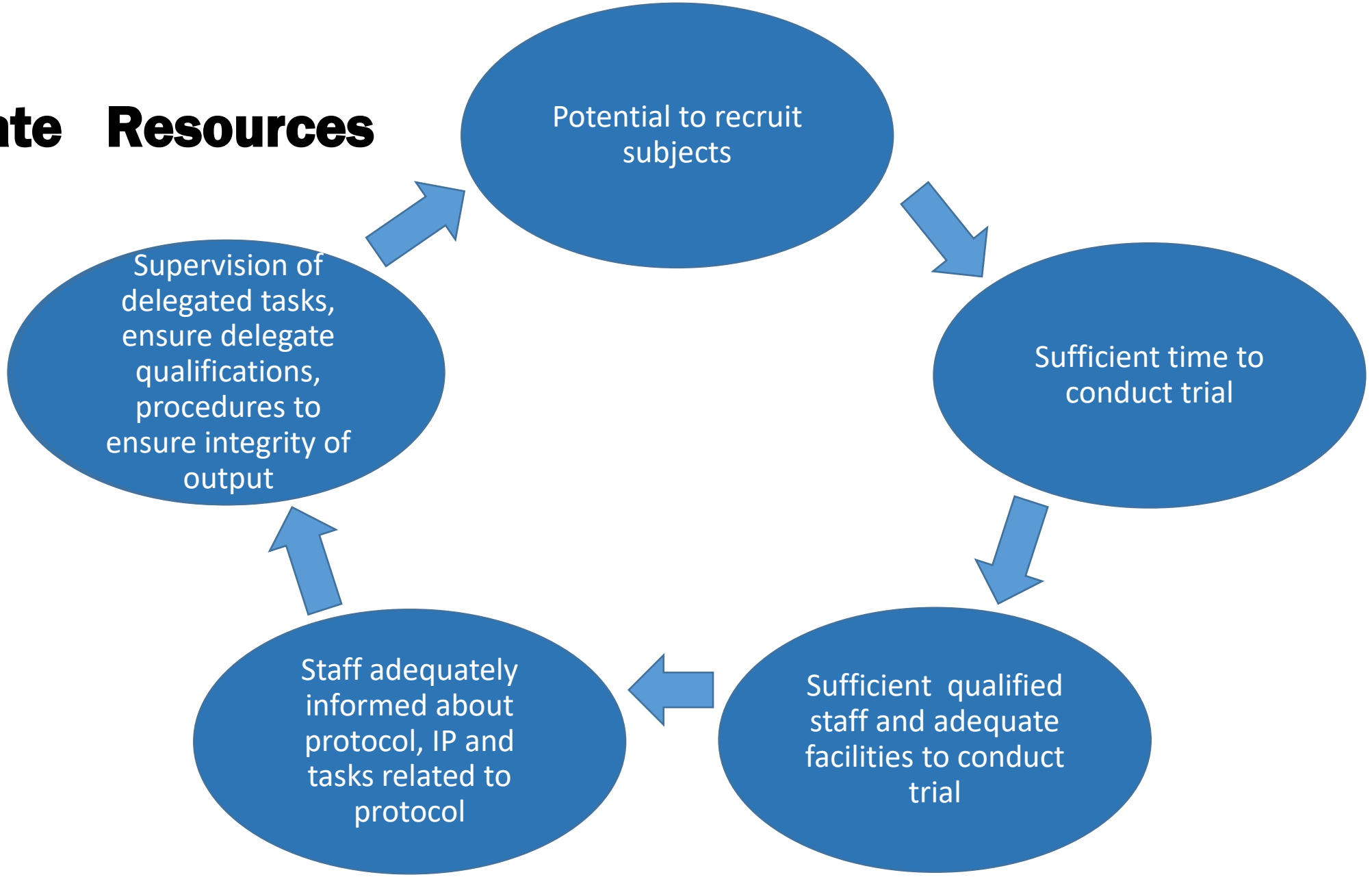
(4.13) Final Reports

4.1 Investigator Qualifications and Agreements

- Investigator qualification
- Demonstrate evidence of adequate training
- Awareness of and compliance with GCP and regulatory requirements
- Investigational product familiarity
- Allow for monitoring/auditing/inspection to enable sponsor/regulatory oversight
- Use of qualified support staff
- Document delegation of duties to appropriately qualified persons

4.2

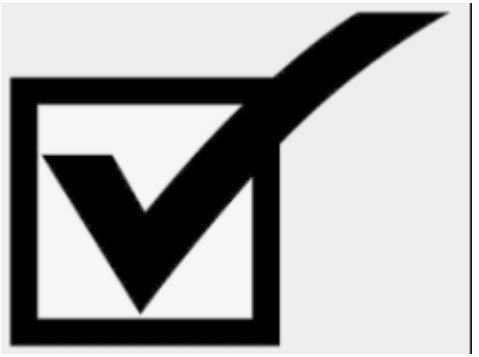
Adequate Resources



Application of GCP

3 out of 4 enrolled subjects at a site did not meet eligibility criteria. When questioned, the PI stated that day-to-day operations were delegated to the CRO. Who is responsible for this compliance issue?

- **The PI**
- **The CRO**
- **The Sponsor**
- **All of the above**



4.3 Medical Care of Trial Subjects

- Qualified physician or dentist who is an investigator or sub-investigator should be responsible for all trial related medical decisions
- During and following the trial, the investigator/institution should ensure appropriate medical care for AEs and clinically significant lab deviations related to trial and inform subjects if medical care is needed for intercurrent illness
- It is recommended that the Investigator inform the subject's primary physician of subject's participation in trial (after obtaining permission from the subject)
- Physician to make a reasonable effort to ascertain the reasons for subject's premature withdrawal from the trial

4.4 Communication with IRB/IEC

- IRB – independent body responsible to ensure protection of rights, safety, and well-being of human subjects
- Before trial begins, obtain written, dated approval/ favorable opinion for protocol and all documents provided to subjects (e.g. ICF, advertisements)
- Provide a copy of Investigator's Brochure/updated IB
- Before and during the trial, provide all documents required by IRB/IEC for review and appropriate approval/ favorable opinion

4.5 Compliance with Protocol

- Conduct trial according to approved protocol, GCP and applicable regulatory requirements
- Document the acceptance to follow protocol in a protocol signature page or contract
- Protocol deviation process - no deviations or changes prior to sponsor and IRB/IEC approval/ favorable opinion

– Exception: Deviation necessary to eliminate immediate hazard

*Deviations need to be documented and rationale submitted to sponsor, IRB/IEC and regulatory authorities

4.6 Investigational Products

- Responsibility for IP (Investigational Product) accountability & delegation of activities and supervision of an appropriately qualified person
- Documentation of delivery, inventory, dispensation, usage, disposal or return and reconciliation of all IP and other study medication
- Stored per requirements
- IP usage per protocol
- Explanation of correct use of IP to subjects and periodic check for understanding/compliance

4.7 Randomization Procedures and Unblinding

- Follow the trial's randomization procedures

- Blinded trials: Promptly document and report to sponsor any premature unblinding

4.8 Informed Consent of Trial Subjects

Process	Form
IRB approval prior to use of written consent other written information	Subject informed of all pertinent aspects of the trial prior to participation
Informed consent discussion needs to include all relevant explanations	Informed consent form needs to include all relevant explanations
Language used in oral information/consent should be understandable	Language used in written information/consent should be understandable
Subject should have ample time to review the ICF, ask any questions, and receive answers before decision is made	Subject should be aware that withdrawal is possible at any time
Subject should not be unduly influenced to participate	Subject should not be asked to waive legal rights or release investigator/sponsor from liability for negligence
ICF obtained/signed prior to subject's participation in a trial	ICF obtained, signed/dated by subject prior to participation in a trial. Person obtaining consent must sign/date ICF
Copy of signed and dated ICF to subject/LAR prior to participation in a trial. Includes any other written information	ICF must be updated/approved when new info available that may be relevant to subject's consent

Informed Consent
Special Populations

- When a subject can only be enrolled with the consent of the LAR, subject must be informed to the level of their understanding, provide assent (where this is feasible) and personally sign and date the consent form
- In emergency situations where subject and legal representative are unable to consent, enrollment requires protective measures to be described in protocol/other IRB/IEC approved documents. Subject or legal representative should be informed as soon as possible and consent to continue and other consent as appropriate
- If the subject/legal representative is unable to read, an impartial witness must be present during the consent discussion and sign/date consent form
- Under certain circumstances, nontherapeutic trials may be conducted with consent of LAR

Application of GCP

- PI provides info about a study to faculty, residents and staff at departmental meeting
- Hands out IRB approved flyers to be given to patients
- Flyer instructs patient to contact PI if interested
- Interested patient calls PI from clinic
- PI is unable to go to clinic to talk about study and consent
- Study coordinator also not available
- PI instructs patient to wait at clinic
- PI calls resident who was present at departmental meeting and emails resident blank consent form
- PI instructs resident to consent the patient

Is this recruitment and consent method appropriate?

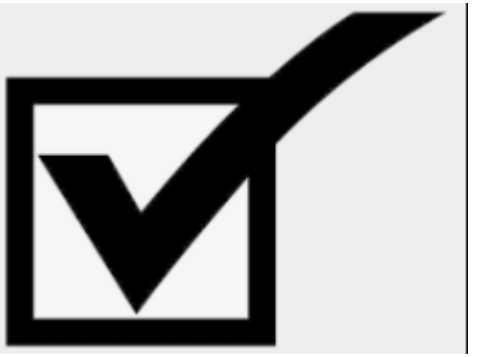
- Yes
- No

Application of GCP

Dr. Who, an investigator on a multi-center phase 3 drug trial has some very experienced staff. He is filling out the delegation log for his senior research coordinator, Justin Bieber, MPH, who has 10 years of experience working in clinical research.

Activities to be delegated:

1. Recruitment and phone screening of study subjects
2. Involvement in the informed consent process, including review of the consent form with subjects (with a study doctor involved to answer any medical questions)
3. Independent assessment of AEs
4. Giving the neuropsychological testing battery, after training and competence assessment
5. Assessment of eligibility criteria including clinical measures
6. Physical exam



What study activities could be delegated to Justin?

Response options:

- All activities can be delegated
- Activities 1 and 2 can be delegated
- Activities 1, 2, 3 can be delegated
- Activities 1, 2 and 4 can be delegated
- Activities 1, 2, 3, 4, 5 can be delegated

4.9 Records and Reports

- Adequate source documents and trial records for each trial subject
- Retention of essential documents
- CRFs and all required reports (written or electronic)
  - Accuracy, legibility, completeness of data
  - Data to be consistent with source data
- Corrections are dated & initialed, do not obscure original entry and explained if necessary (applies to written and electronic changes/updates). Retain records of changes and corrections
- Financial aspects documented in an agreement between sponsor and investigator/institution
- Direct access to all trial-related documents by the monitor, the auditor, the IRB/IEC or regulatory authority.

4.10 Progress Report

- Investigator submits written summaries of progress to IRB/IEC at least annually or as required
- Provide written reports to sponsor and IRB/IEC (and institution where required) of any significant changes affecting the study or increased risk to subjects

4.13 Final Report

- Upon completion of trial, provide sponsor with all required reports
- Final report with a summary of trials & outcomes submitted to IRB/IEC and regulatory authorities as required

4.11 Safety Reporting

- AE Reporting
  - All AE and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor within the time period defined in protocol
- All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g. Investigator's Brochure) identifies as not needing immediate reporting
  - Prompt follow up with detailed written reports
  - Subjects should be identified by unique code numbers
  - Report unexpected serious drug reactions according to regulatory and IRB/IEC requirements
  - Sponsor and IRB/IEC may need additional information for reported deaths (e.g. autopsy report)

4.12 Premature Termination or Suspension of Trial

- Responsibility to promptly inform the trial subjects and ensure appropriate therapy and follow-up. Inform regulatory authorities when required

- Responsibility for communication of study termination or suspension of study to sponsor, IRB/IEC and institution as applicable, including a detailed written explanation

Non-compliance with GCP

- Poor supervision and training of study staff
- Insufficient investigator involvement in study conduct
- Inappropriate delegation of study tasks to unqualified persons
- Overworked investigator and study staff (too many subjects, complex study with large data collection, too many concurrent studies)
- Protocol deviations (eligibility criteria, study schedule, dosing…)
- Inadequate documentation (consent, study records, IP tracking…)
- Inadequate/untimely reporting of AEs

Summary

Principles of GCP

- Ethics
- Protocol and Science
- Responsibilities
- Informed Consent
- Data Quality and Integrity
- Investigational Products
- Quality Control/Quality Assurance

Roles and Responsibilities of PI/Study Staff

- Qualified PI and Staff
- Adequate Resources
- Medical Care of Subjects
- Communication with IRB
- Compliance with IRB approved research
- Investigational Product
- Randomization and Unblinding
- Informed Consent
- Records and Reports
- Premature Termination

ICH-GCP E6(R2) Guideline for Good Clinical Practice - https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

Institutional links to training requirements (including GCP)

- BU/BMC:
  - http://www.bumc.bu.edu/ohra/required-training/
- UVM:
  - https://www.uvm.edu/rpo/human-subjects-research
  - https://www.uvm.edu/rpo/irb-policies-and-procedures#training_II
- UF:
  - http://irb.ufl.edu/index/requiredtraining.html
- MUSC:
  - https://horseshoe.musc.edu/research/citi