Good Clinical Practice

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ASQ

Disclaimer

The views expressed in this presentation are those of the presenter and do not necessarily represent the official position of the FDA.

Good Clinical Practice

A set of standards to assure that:

- The rights, safety and well being of trial subjects are protected
- The data and reported trial results are credible and accurate

ICH E-6 GCP Guidance (1996)

FDA Guidance: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring (2013)

Early History of GCP

- Early GCP documents were responses to dramatic failures of human subject protection:
  - Nuremberg Code (1947)
    http://www.hhs.gov/ohrp/archive/nurcode.html
  - Declaration of Helsinki (1964, with several later amendments)
    http://www.wma.net/en/30publications/10policies/b3/17c.pdf
- Neither of these had the force of law in the US

US Experience: Tuskegee Syphilis Experiment

- Sponsored by USPHS and Tuskegee Institute; conducted from 1932 - 1972
- Goal was to understand the natural history of syphilis to support increased treatment efforts for African-Americans (AA)
- Enrolled 600 AA men – 399 with syphilis, 201 without it
- No informed consent
- Subjects told they were being treated for “Bad Blood”

Tuskegee Syphilis Experiment

- Penicillin therapy for syphilis began in mid 1940s
  - USPHS syphilis treatment program began in 1947, but Tuskegee subjects were not informed or treated
- Press story regarding experiment in 1972 led to review of the study by a Federal Advisory Panel
- Panel found that subjects entered freely but were not given facts required to provide informed consent

Tuskegee Syphilis Experiment

- Panel concluded the study was “ethically unjustified”
- The HHS Ass’t Secretary for Health and Scientific Affairs ended the study in late 1972
  - A class-action lawsuit was brought on behalf of study subjects in 1973
  - A 1974 settlement and Act of Congress provided for lifetime and burial benefits for participants; in 1975 widows and offspring were added to the program
  - http://www.cdc.gov/tuskegee/

National Research Act – 1974

- Created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- Belmont Report (1979) summarizes the 3 principles identified by the Commission -
  - Respect for persons: persons are autonomous agents except when they have reduced capacity for self-determination, when they might need special protection
  - Beneficence: do no harm, maximize possible benefits, minimize possible risks
  - Justice: selection of research subjects, availability of fruits of public funds to those who might not afford them

http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html

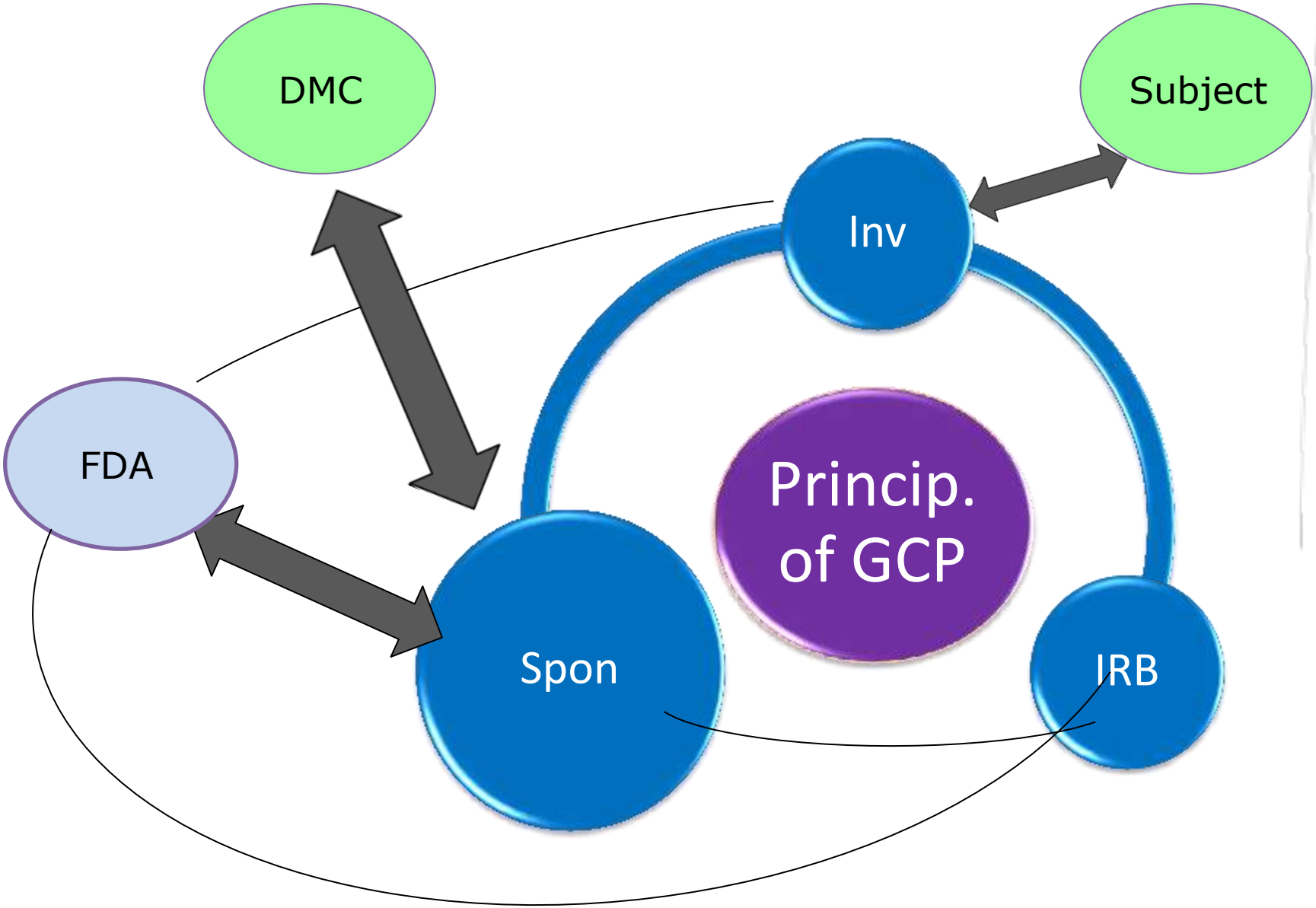
Regulatory Response

- Belmont Report led to FDA Rule on Protection of Human Subjects (21 CFR part 50, 1980) and similar regulations for Federally sponsored research in 45 CFR

ICH Guidelines for Good Clinical Practice (E6)

- Adopted by the ICH parties in 1996
- Adopted as an FDA Guidance in May 1997
- Applies to clinical trials that are intended to be submitted to regulatory authorities

The Network of GCP



Section 3

Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC)

Institutional Review Board (IRB)

- An independent body constituted of medical, scientific, and non-scientific members
- Its responsibility is to ensure the **protection of the rights, safety and well-being of human subjects** involved in a trial by:
  - Reviewing and approving key trial documents
  - Reviewing the submitted reports of serious and unexpected adverse events
- Should pay special attention to trials that may include vulnerable subjects.

IRB/IEC Responsibilities

- The IRB/IEC should be provided with all documents related to the clinical trial, including:
  - Key trial documents
    - trial protocol(s)/amendment(s)
    - written informed consent form(s)
    - Investigator's Brochure (IB)
  - Subject recruitment procedures
  - Available safety information
  - Information about payments to subjects

IRB/IEC Responsibilities

- The IRB/IEC:
  - Considers the qualifications of the investigator for the proposed trial
  - Conducts initial and continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

IRB/IEC Responsibilities

- If prior consent of the trial subject or the subject's legally acceptable representative (LAR) is not possible (i.e. in emergency situations), the IRB/IEC should determine that the proposed protocol:
  - Adequately addresses relevant ethical concerns
  - Meets applicable regulatory requirements for such trials.

IRB/IEC Responsibilities

- Review of the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects.

IRB/IEC Functions and Operations

- The IRB/IEC performs according to written operating procedures, and maintains written records of its activities and minutes of its meetings.
- The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.
- An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

IRB/IEC Procedures

- **No subject should be admitted to a trial before the IRB/IEC issues its written approval of the trial.**
- **No deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval** except when
  - It is necessary to eliminate immediate hazards to subjects
  - The change(s) involves only logistical or administrative aspects of the trial

IRB/IEC Procedures

- The investigator should promptly report to the IRB/IEC:
  - Deviations from, or changes of, the protocol to eliminate immediate hazards
  - Changes increasing the risk to subjects and/or affecting the conduct of the trial.
  - All adverse drug reactions (ADRs) that are both serious and unexpected.
  - New information that may affect adversely the safety of the subjects or the conduct of the trial.

Section 4

Investigator

Investigator

- The investigator is the 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 is usually called the principal investigator.
- A subinvestigator is a member of the clinical trial team supervised by the investigator who is designated to perform critical trial-related procedures and/or to make important trial-related decisions.

Clinical Trial Site

- Academic Medical Center
- Hospitals
- Group clinics
- Private offices
- Clinical research centers

Investigator Selection

- Initial contact by the sponsor or CRO
- Confidentiality agreement
- **Pre-trial site visit is advisable**
- Evaluation and acceptance of the investigator by the sponsor
- Contract

Qualifications of the Clinical Investigator

- An appropriately qualified person in the relevant field of health care (MD, PhD, PharmD, nurse)
- Trained and experienced in the therapeutic area and in clinical research
- **Knowledge of GCPs**
- Good understanding of regulatory requirements
- Good record-keeping practices

Drug Supply

- The person who handles the drug supplies is one of the most important at any site
- Usually a pharmacist
- Site is responsible for following the Sponsor's instructions on proper drug storage

Responsibilities of the Clinical Investigator

- Familiar with the background of the study (e.g., disease, management of the disease, expected side effects of similar treatment)
- Familiar with the study, the protocol document, and study procedures
- **Comply with all procedures specified in the protocol in accordance with GCP**

Responsibilities of the Clinical Investigator

- Obtain approval of the protocol and the informed consent form from the Institutional Review Board (IRB) prior to the initiation of the study
- Obtain informed consent from the patient or the Legally Acceptable Representative (LAR) prior to starting protocol treatment or randomization
- Provide information about protocol progress to the IRB on a regular basis

Responsibilities of the Clinical Investigator

- Maintain all study documentation
- Perform data verification
- Match case report forms with source data
- Make data available for external monitors

Delegation

The PI may delegate tasks to sub-investigators but he/she is responsible for compliance with GCPs

(Section 4 continued)

Informed Consent

ICH GCP Definition of Informed Consent

- Informed consent is a process:
  1. The subject is informed of all aspects of the trial that are relevant to the decision to participate. The language used should be understandable to the subject
  2. The subject voluntarily confirms his or her willingness to participate in a particular trial
  3. Informed consent is documented by means of a written, signed, and dated informed consent form.
- The investigator is responsible for obtaining informed consent

Informed Consent of Trial Subjects - Specific Requirements

- The written informed consent form and any other written information to be provided to subjects is revised whenever important new information becomes available.
- Any revisions should receive the IRB/IEC's approval in advance.
- **The subject should be informed if new information becomes available that may be relevant to the subject's willingness to continue.**

Informed Consent of Trial Subjects

- Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.
- None of the oral and written information concerning the trial should contain any language that:
  - Causes the subject to waive or to appear to waive any legal rights
  - Releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

Informed Consent of Trial Subjects

- Minors and adults unable to read or comprehend the consent form may enroll if a legally acceptable representative (LAR) gives consent.

Informed Consent of Trial Subjects - Contents

- Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:
  - That the trial involves research.
  - The purpose of the trial.
  - The trial treatment(s) and the probability for random assignment to each treatment.
  - The trial procedures to be followed, including all invasive procedures.

Informed Consent of Trial Subjects - Contents

- The subject's responsibilities.
- **Those aspects of the trial that are experimental.**
- **The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.**
- **The reasonably expected benefits.**

Informed Consent of Trial Subjects - Contents

- **Any alternatives that may be available to the subject, and their important potential benefits and risks.**
- The compensation and/or treatment available to the subject in the event of trial-related injury.
- The anticipated prorated payment, if any, to the subject for participating in the trial.
- The anticipated expenses, if any, to the subject for participating in the trial.

Informed Consent of Trial Subjects - Contents

- **That the subject's participation in the trial is voluntary and that the subject may withdraw from the trial, at any time, without penalty.**
- **That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject**.

Exemption From Informed Consent (EFIC)

21 CFR 50.24 allows EFIC if an IRB finds that:

- The subject's life is threatened, available therapy is not satisfactory or proven, and collection of evidence is necessary to determine safety and efficacy of the test therapy
- Obtaining consent is not feasible because of the patient's medical condition, and immediate intervention is required, and a legal representative is not available in a timely manner
- AND the study could not practicably be conducted without a waiver
- AND the study is monitored by a independent data monitoring committee.

Summary

- **Informed Consent**
  - **<u>Is an educational process that takes place between the investigator and the prospective subject.</u>**
    - Starts by informing a potential study subject and continues throughout the study
    - Requires disclosure of information, adequate comprehension, and a voluntary decision to participate
  - **<u>Is not simply a form to be signed</u>**
  - **<u>Is not a single event</u>**

Section 5

Role of the Sponsor

Sponsor

- An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Quality Assurance and Quality Control

- **The Sponsor is responsible for implementing and maintaining quality systems to ensure that trials are conducted and data are generated, documented and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).**

Contract Research Organization (CRO)

- A sponsor may transfer any or all of their trial-related duties and functions to a CRO in a written document
- The ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor, but --
- If functions are transferred to a CRO, the CRO shares responsibility with the Sponsor for the GCP obligations related to those functions

Trial Design, Data Handling, and Record Keeping

- The sponsor should utilize appropriately qualified individuals:
  - Design the trial and trial documents
  - To handle the data,
  - To verify the data,
  - To conduct the statistical analyses, and
  - To prepare the trial reports.
- **The sponsor may consider establishing an independent data-monitoring committee (DMC) to assess the progress of a clinical trial**

Investigator Selection

- Before entering an agreement with an investigator to conduct a trial, the sponsor should provide the investigator(s) with
  - the protocol
  - an up-to-date Investigator's Brochure

Investigator Selection

- **The sponsor should obtain the investigator's agreement:**
  - **to conduct the trial in compliance with GCP and**
    - **the applicable regulatory requirement(s)**
    - **the protocol agreed to by the sponsor and approved by the IRB/IEC.**
  - **to comply with procedures for data handling;**
  - **to permit monitoring, auditing and inspection and**
  - to retain the trial related essential documents as needed.
- The sponsor and the investigator should sign the protocol to confirm this agreement.

Compensation to Subjects and Investigators

- The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

Confirmation of Review by IRB/IEC

- The sponsor obtains from the investigator:
  - A statement obtained from the approving IRB/IEC that it operates according to GCP and the applicable laws.
  - Documented IRB/IEC approval
  - Any written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects.

Information on Investigational Product(s)

- The sponsor should update the Investigator's Brochure as significant new information becomes available.

Manufacturing, Packaging, Labeling, and Coding Investigational Product(s)

- The sponsor should ensure that the investigational product(s) are:
  - characterized as appropriate to the stage of development of the product(s)
  - manufactured in accordance with any applicable GMPs
  - coded and labeled in a manner that protects the blinding.
- The sponsor determines and describes:
  - Storage conditions and times
  - Drug administration procedures and associated fluids and devices

Supplying and Handling Investigational Product(s)

- **The sponsor should not supply an investigator with the investigational product(s) until the sponsor obtains all required documentation, including documentation of IRB approval**
- The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor).

Safety Information

- The sponsor should promptly notify all concerned investigator(s), to IRBs (where required) and the regulatory authority(ies) of findings that could:
  - Affect adversely the safety of subjects
  - Impact the conduct of the trial
  - Alter the IRB/IEC's approval to continue the trial.
  - These findings include all adverse drug reactions that are both serious and unexpected
- The sponsor should submit all safety updates and periodic reports, per regulatory requirement(s).

Monitoring

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

Extent and Nature of Monitoring

- The sponsor should ensure that the trials are adequately monitored and should determine the extent and nature of monitoring.
- This should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial.
- *There is a need for on-site monitoring, before, during, and after the trial*

Monitor's Responsibilities

- The monitor(s) should ensure that the trial is conducted and documented properly by carrying out the following activities when necessary:
  - **Acting as the main line of communication between the sponsor and the investigator.**
  - **Verifying that the investigator has adequate qualifications and resources and remain adequate throughout the trial period**
  - **Verifying, for the investigational products (IP) are stored, dispensed and returned properly and that patients are properly instructed regarding IP**

Monitor's Responsibilities

- Verifying that the investigator follows the approved protocol and all approved amendment(s) with respect to enrollment criteria and study procedures.
- Verifying that written informed consent was obtained before each subject's participation in the trial.
- Ensuring that the investigator receives
  - the current Investigator's Brochure,
  - all documents
  - all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

Monitor's Responsibilities

- **Verifying that trial records are accurate, complete, kept up-to-date and maintained.**
- Reporting the subject recruitment rate.
- Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other, with special attention to -
  - **Any dose and/or therapy modifications**
  - **Adverse events, concomitant medications and concurrent illnesses**
  - **Withdrawals and dropouts of enrolled subjects (including explanations for these events)**
  - **Verification of endpoint events**

Monitor's Responsibilities

- Informing the investigator of any entry error, omission, or illegibility. The monitor should ensure that corrections are made, dated, explained, and initialed by the investigator or by trial staff.
- Determining whether the investigator is maintaining all essential documents.
- **Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator**
- **Taking appropriate action designed to prevent recurrence of the detected deviations**

Monitoring Report

- **The monitor should submit a written report to the sponsor after each trial-site visit or communication.**
- Reports should include a summary of what the monitor reviewed and statements concerning the:
  - Significant findings/facts
  - Deviations and deficiencies
  - Conclusions
  - Actions taken or to be taken
  - Actions recommended to secure compliance.
- The review and follow-up of the monitoring report should be documented.

Audits

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

Auditing Procedures

- The observations and findings of the auditor(s) should be documented.
- Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.

Noncompliance

- **Noncompliance with the protocol, SOPs, GCP, and/or regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action to secure compliance**.
- **Serious or persistent non-compliance should trigger termination of the investigator from the trial**
- **When an investigator's participation is terminated, the sponsor should notify promptly the regulatory authority(ies).**

Premature Termination or Suspension of a Trial

- If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators and the regulatory authority(ies) of the reason(s) for the termination or suspension.
- The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension.

Clinical Reports

- The Sponsor should prepare clinical trial reports and provide them to regulatory agencies as required by the applicable regulatory requirement(s)
- Reports should be written in compliance with the ICH Guideline for Structure and Content of Clinical Study Reports.
- The above applies regardless of whether the trial is completed or prematurely terminated.

Section 7 – Investigator's Brochure (IB)

- The IB is a compilation of data that is relevant to the study of the product in humans
  - Purposes - to provide investigators with:
    - Information regarding the rationale of key protocol features to facilitate compliance with the protocol
    - Information to support clinical management of subjects during the study
- Appendix 2 of the Guidance describes contents of the IB in a model Table of Contents
- *For marketed products, a package insert may suffice in lieu of an IB*

Section 8 - Essential Documents for the Conduct of a Clinical Trial

These are documents that permit evaluation of the trial conduct and data quality and serve to demonstrate compliance with GCP and regulatory requirements

- **Are kept at the Sponsor's site and/or investigational sites and should be available for audit**
- Relate to the 3 temporal study phases:
  - Before the Clinical Phase of the Trial (e.g., protocol, IB, sponsor - investigator agreements, IRB approvals)
  - During the Clinical Conduct of the Trial (e.g., signed consent forms, study drug shipping records, monitoring reports, source documents, serious AE reports sent to sponsor and IRB)
  - After Completion or Termination of the Trial (e.g., drug accountability records, trial close-out monitoring reports)

ICH-GCP link and CFR cites

- http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf
  - Section 1 has an excellent glossary of terms
- For more US GCP information, see in 21 CFR:
  - Part 50 (informed consent)
  - Part 54 (financial disclosure)
  - Part 312.50 to 312.59 (obligations of sponsors)
  - Part 312.60 to 312.70 (obligations of investigators)

Challenge Question 1

Under ICH GCP, a Sponsor may ship study drug to a site if the site has stated in writing that it will not dispense the drug until they have IRB approval to proceed with the study

A. True

B. False

Challenge Question 2

Informed Consent may be waived for studies requiring emergency treatment -

A. Never
B. If FDA gives written permission
C. If the sponsor monitors enrollment violations frequently and provides monitoring reports to FDA
D. If the trial could not otherwise be conducted and if applicable regulatory requirements for such trials are met.
E. If B and C are both true