Good Clinical Practices

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Good Clinical Practices

- FDA 21 CFR
- Electronic docs (11)
- Informed Consent (50)
- $ disclosure (54)
- IRBs (56)
- IND regs (312)

GCPs

- HHS 45 CRF 46
- IRBs (Subpart A)
- Informed consent (A)
- Women (B)
- Prisoners (C)
- Children (D)

ICH E6
- IRBs (3)
- Investigator (4)
- Sponsor (5)
- Protocol (6)
- IB (7)
- Essential docs (8)
Why regulate clinical trials?

- To ensure the rights, safety, and well-being of human subjects participating in research

- To provide useful scientific data to improve or change the standard of care
A standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials that provide assurance that the data and reported results are credible, accurate and that the rights, integrity and confidentiality of trial subjects are protected.
Goal of the ICH is to harmonize the requirements to obtain drug approval in US, Europe and Japan

Typically referring to Section E6 – Good Clinical Practices, first published in 1996

Recent Revision - ICH GCP E6 R2 – Step 4 – November 2016
Amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording, and reporting while continuing to ensure human subject protection and reliability of trial results.

Supplements existing guidance with additional text to provide more details on individual topics:
- Risk-based monitoring
- Data integrity
- Quality management
ICH GCP Guideline – 8 sections

1. Glossary of Terms
2. Principles of GCP
3. Requirements for IRB/EC
4. Requirements for Investigators
5. Requirements for Sponsors
6. Requirements for clinical trial protocol and protocol amendments
7. Responsibilities of a Sponsors to develop an Investigator’s Brochure
8. Essential Documents
Definitions

- **Sponsor**: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial
  - Focus on *overall study objectives*
  - Responsibility of reporting to FDA and IRB

- **Investigator**: A person responsible for the conduct of the clinical trial at a trial site
  - Focus on *subjects* and implementation of study protocol
  - Responsibility of Investigative site with reporting to IRB and Sponsor
Sponsor- Investigator

- An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

   Wearing both “hats” can be challenging
Academic Trial Sponsors

- Regulatory “sponsor” – person who submits IND application to FDA
- Financial “sponsor” – funding source (NIH, industry collaborator, foundation, etc)
- Coordinating Center – team that assists academic PI to fulfill all regulatory requirements of managing clinical study
When do ICH Guidelines Apply?

- Studies conducted in the US which are intended to be marketed in ICH regions
- Studies conducted in ICH regions which intend to submit results to the FDA for approval in the US
Many Trials are Conducted Globally...
Drug Discovery and Development

Pre-Clinical Research and Development

Clinical Trial

FDA reviews NDA

Manufacturing

IND Submitted

NDA Submitted

FDA Approval

2-10 years

3-6 years

1-2 years

6-7 years

Initial Synthesis of Substance

Laboratory Studies and Animal Testing

Institutional Review Boards

Research and Development (all trails approved by IRB)

Phase One - Testing in Healthy Subjects

Phase Two - Testing in Individuals with the Disease

Phase Three - Larger scale testing in individuals with the Disease

FDA Expects Review Data

Company Address FDA Concerns

Advisory Hearing maybe called

Drug appears on the Market

Post Market Surveillance

Follow up Studies and Inspections

FDA = US Food and Drug Administration
IND = Investigation New Drug
NDA = New Drug Application
Quality & Delegating Tasks

- **Quality Assurance and Quality Control**
  - Implement and maintain QA and QC systems with written SOPs
  - **Use risk-based approach to quality management systems**

- **CRO**
  - Any trial-related duties and functions transferred to a CRO should be specified in writing
  - **Oversee trial-related duties subcontracted to a CRO**

- **Medical Expertise**
  - Designate appropriately qualified medical personnel to advise on trial related medical questions or problems
Trial Design & Management

- **Trial Design**
  - Utilize qualified individuals for all stages of trial process (design, CRF design, data analysis, study reports, etc)

- **Trial Management, Data Handling, Record Keeping, and Independent Data Monitoring Committee**
  - Utilize qualified individuals to handle, verify and conduct analysis of data
  - When using electronic data handling, ensure EDC is validated, secure, permits changes, maintain SOPs for system, maintain audit, data and edit trails
  - **When using computerized systems, base validation approach on a risk assessment, maintain SOPs and ensure data integrity**
Site Selection and Contracting

- **Investigator Selection**
  - Select trained and qualified investigators/institutions

- **Compensation of Subjects and Investigators**
  - Provide insurance of indemnification to investigator/institution
  - Establish policies and procedures addressing costs of treatment of subjects in event of trial-related injury
Regulatory Submissions

- Regulatory submissions:
  - Submit required applications prior to initiation of a study (FDA)

- Confirmation of Review by IRB
  - Obtain IRB name, address and assurance number
  - Obtain IRB approval letters for all submissions (initial protocol, amendments, continuing review, etc)
Investigational Product (IP)

- Information on the IP
  - Update Investigator’s Brochure (IB) as significant new information becomes available

- Manufacturing, Supply and Handling IP
  - Collect and maintain documentation of GMP manufacturing
  - Supply to sites only after all regulatory documents collected
  - If blinded study, create systems that ensure study blind
  - Ensure timely delivery and re-supply
Safety Information
- Responsible for ongoing safety evaluations
- Promptly notify investigator/institution, and appropriate regulatory authorities of findings that could adversely affect subject safety

Adverse Drug Reaction Reporting
- Expedite reporting of all adverse drug reactions (ADRs) that are both serious and unexpected
- Submit safety updates and periodic reports per applicable regulatory requirements
Monitoring

- Ensure that trial data are accurate, complete and verifiable
- Ensure trial conducted in compliance with protocol, GCP and other applicable regulatory requirements
- **Develop a systematic, prioritized, risk-based approach**
- **Develop a monitoring plan tailored to the human subject protection and data integrity risks of the trial**
- **May use varied approaches to monitoring (on-site, centralized) to improve effectiveness and efficiency**
- **Document the rationale for the monitoring strategy**
- **Document results of monitoring activities**
Non-Compliance/ Audits

- **Noncompliance**
  - Act quickly in situations of noncompliance
  - Terminate investigator’s participation in cases of persistent noncompliance
  - **Follow up of non-compliance that has or may significantly affect human subject protection or reliability of trial results, by performing a root cause analysis and implementing preventative actions**
Suspension / Termination and Reporting Requirements

- **Premature Termination or Suspension of Trial**
  - If required, promptly inform the investigators/institutions, and regulatory authorities and describe reasons
  - Provide instruction to sites to notify their local IRB of the action

- **Clinical Trial/Study Reports**
  - Prepare reports and provide to appropriate regulatory authorities
Multicenter Trials

- Multicenter Trial
  - Ensure all investigators conduct trial in strict compliance with the protocol approved by Sponsor, regulatory authorities and IRB
  - CRFs are designed to capture the required data at all multicenter trial sites.
  - The responsibilities of the coordinating investigator(s) and other participating investigators are documented prior to the start of the trial
  - All investigators are given instructions on following the protocol, complying with a uniform set of standards for assessments and completing CRFs
  - Communication between investigators is facilitated
Investigator Obligations
Responsibilities

- Site Investigator Responsibilities (21CFR 312.60)
  1. Protect the Rights, Safety, and Welfare of study subjects
  2. Ensure that the investigation is conducted according to the approved protocol and applicable regulations (Federal, State, Local)
  3. Control drugs, biologics, and devices under investigation (312.61)

Most but not all of these requirements are listed in FDA-1572 Form
KEEP CALM AND TAKE THE RESPONSIBILITY
1. Provide **reasonable medical care** for study subjects for medical problems that are, or could be, related to study intervention

2. Provide **reasonable access** to medical care
   - The investigator should be available 24/7 to subjects during the conduct of the trial

3. **Adhere to the protocol** so that subjects are not exposed to unreasonable risks, examples:
   - Failure to adhere to I/E Criteria: enrolling subject with renal failure in trial excluding people with renal failure because the investigational drug may be nephrotoxic
   - Omitting a safety measure: CBC for a therapy that causes neutropenia
   - Site investigator should inform the subject’s primary physician about the subject’s participation in the trial, if the subject agrees
When tasked are delegated, the investigator is responsible for

1. Choosing **qualified** individuals to perform delegated tasks
2. Providing **adequate training** for the delegated tasks and for study protocol

Commonly inappropriately delegated tasks identified by FDA inspections:

- Screening evaluations (medical history, assessment of I/E criteria)
- Physical exams
- Evaluation of AE’s
- Assessments of primary study endpoints
- Obtaining informed consent

'The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.'
Delegation – FDA Guidance
Adequate Training

Investigator should ensure that site staff:

- Are familiar with the **purpose** of the study and the protocol

- Have an adequate understanding of the specific details of the **protocol** needed to perform their assign tasks (FVC)

- Are aware of the **regulatory requirements** and acceptable standards for conduct of clinical trials and protection of human subjects (GCP)

- Are **competent** to perform the tasks (ECG, VS, FVC)

- Are **informed** of any pertinent protocol changes
Site Investigator should have sufficient time to properly conduct and supervise the clinical trial.

**FDA** identified factors that may affect the ability of an investigator to provide adequate supervision:

1. Inexperienced study staff
2. Demanding workload for study staff
3. Complex clinical trials
4. Large number of subjects enrolled at the site
5. Seriously ill subject population
6. Conducting multiple studies concurrently at the site
7. Conducting a study from a remote (e.g., off-site) location
Site Investigator should develop a supervision plan

- Routine **meetings** with study staff (trial progress, protocol updates, AE’s, etc.)
- **Documenting** the performance of delegated tasks (delegation log – CV, Training)
- A procedure for ensuring proper **consenting** (consenting check list, note)
- A procedure for ensuring that **source data** are accurate, updated & original (review)
- A procedure for ensuring accurate **match** between source docs and CRFs (review)
- Meetings with **Study Monitor** and a procedure for dealing with queries (check list)
- A procedure for addressing **medical and ethical issues** that arise during the trial (keep Sponsor, IRB and MM informed)
You are Responsible
Site selection

- Pre-selection site questionnaire
  - Number of patients in clinic
  - Number of patients that may fulfill the inclusion/exclusion criteria
  - IRB process and timelines
  - Contracts process and timelines
  - Site PI and CRC/RN experience

- Important Factors
  - Accurate information
  - Reasonable estimates
  - Respond quickly!
Site Activation Checklist

- Contract: Fully executed Clinical Trial Agreement (CTA) (3+ months)
- IRB approval letter of current protocol and ICF (4+ months)
- Investigator’s signature on protocol and IB
- Signed and dated FDA 1572
- Financial disclosures for all study staff on 1572
- IRB membership list
- Human Subject Protection Training Certification (CITI)
- Training: Protocol, Outcome measures, and EDC trainings
- Investigators Meeting
- Site Initiation Visit

Atassi N et al. Neurology 2013
Enrollment

- Recruitment tools (IRB approved)
  - Letters
  - Website
  - Patient database

- Consenting
  - Information – Comprehension – Volunteering
    - Why are we conducting the trial?
    - What happens in this trial?
    - What are the Risks? And what’s the Risk:Benefit Ratio?
    - Who is conducting this research? and who to contact?
  - Ongoing process
  - ICF: signatures, date, time, copies

- Screening and Randomization
  - Eligibility check list, signed by PI
  - Randomization note signed by PI
Follow up Visits

- **Guidance:** Protocol, IB, and Study Monitor
- **Visits (SOA)**
  - Within window
  - Complete assessments
  - **Safety first** (labs, AEs, SAEs, PDs)

- **Source and CRF’s clear and clean**
  - *Document Document Document

  *‘Not Documented = Never Happened’*

- Data entry up-to-date
- Monitoring visits (prepare, meet, address, follow up)
- Keep your grant manager in the loop
Adverse Events (AE)
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

- Always ask subjects
- Volunteered, prompted, Lab, Physical Exam
- Coding (MedRA vs. CTCAE)
- Date and time of onset and resolution
- Severity?
- Relatedness to study drug(s) or trial procedures
- Expectedness, as listed in the IB at the observed specificity or severity
Serious Adverse Event (SAE)

- Criteria *(in view of investigator or sponsor)*
  - Death
  - Life Threatening (immediate risk of death)
  - Hospitalization or prolong existing hospitalization
  - Persistent or significant inability to conduct normal life functions
  - Congenital anomaly or birth defects
  - Important Medical Events: Require an intervention to prevent the above (ER treatment of allergic reaction, long-term disability, etc.)

- Reporting to sponsor (within 24h)
- Reporting to Site IRB (Per Site IRB rules)
- Follow up
Safety First (3)
21CFR 312.32

- **Labs**
  - Clinical significance
  - Reporting as AE
  - Follow up!

- **Protocol Deviations**
  - ?affect subject safety
    - Missed/delayed safety assessment
    - Missed I/E criterion
    - Con meds (interaction with Investigational Product)
  - ?affect trial integrity
    - I/E, outcome, Disallowed/Investigational meds, Drug accountability, etc.
  - Keep a Log of PD’s
Site Close Out
KEEP CALM
it's
NOT DONE YET
Record Keeping and Retention
21CFR 312.62

- Adequate Records for Disposition of Drug
  - Dates, quantity, and use by subject
  - Fate of unused drug (returned to sponsor, destroyed at site)

- Case Histories
  - Case Report Forms (CRF’s)
  - Supporting forms: ICF, Medical Records, etc
  - Regulatory binder

- Record Retention for 2 years after
  - NDA is approved for the same investigated indication
  - Investigation is discontinued and FDA is notified (No NDA)
Site investigator takes the overall responsibility of the rights, safety, and welfare of study subjects.

Tasks can be delegated to qualifies individuals with appropriate supervision.

Responsibility cannot be delegated.

If not documented, it never happened.

Safety First.

Always maintain good communication with site staff, IRB, study monitor, and trial sponsor.
What happens when an investigator does not follow these guidelines and regulations?

- Human subjects are placed in jeopardy or harm or are harmed
- Public gains distrust of clinical research
- Investigator restrictions or debarment
- Institutions lose FWA, lose federally funded research
- FDA Audits
  - Form 483 - warning
Questions?

DIFERENT PERCEPTIONS OF REALITY IN RESEARCH

MARKETING

LEGAL

ENGINEERING

INVESTIGATOR

SUBJECT

ACCOUNTING

PUBLIC

What glass?

Let me assure our stockholders that the glass is definitely full!

GLASS BROKEN!
Details at eleven.

Do I have to report this to the IRB?!

The glass is half full!

The glass is half empty.

The glass is too big.
(Modify the protocol.)

How much water did the other PIs get?

Is that placebo or the drug?

The glass is vulnerable, and must be provided special protection.

The glass is not regulation. It must be resubmitted with a handle.

FDA

IRB

COORDINATOR