What FDA Expects in a Pharmaceutical Trial

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Center for Drug Evaluation and Research
Disclaimer

• The views expressed in this talk are those of the speaker and not necessarily those of the US Food and Drug Administration (FDA).
Objectives

• Understand the role of science in drug development

• Understand the role of regulation in drug development

• Understand the role of study staff in complying with regulations and implementing continuous improvement
Good Clinical Practice - GCP

Outline of Topics

• GCP: Science and Quality in Clinical Research

• Regulations and Guidances

• FDA Inspection and Metrics
The US public expects pharmaceutical products that are safe and efficacious.

Frances Kelsey, PhD, MD receiving the President’s Award for Distinguished Federal Service from President Kennedy 1962, the same year as the passage of the Kefauver Harris Amendment to the FD&C Act.
Quality in Clinical Research

• **Clinical trial:** an *experiment* to determine whether the product is safe and effective

• **Statistical sampling:** random selection of a target population

• **Unbiased observations:**
  – Product effect (endpoint)
  – AE collection and reporting
Quality: Why We Care

• Lack of quality can lead to underestimation or overestimation of true treatment effect

• Quality can influence the accuracy of safety reporting

• Label: FDA/sponsor agreed communication with stakeholders
Quality in clinical trials is good science and
It’s in the regulations!
Science and Regulation
General Principles of an IND Submission

21 CFR 312.22:

FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety.
Adequate and Well-Controlled Study
21 CFR 314.126

• (a) The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.
GCP: definition

GCP is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected.

ICH E6 1.24
Elements of GCP

• Well designed protocol and FOLLOW IT!
• DOCUMENTATION
• Accurately and completely collect the data
• Analyze the data according to a prespecified plan
• Accurately report results
Consider these.....

• Adequate resources
• Well trained staff
• Culture of excellence-no fraud or cutting corners
• Understanding of science of clinical trials
## FDA Regulations

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## CDER Regulations

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Goal of Drug Development

• Provide **safe and effective** medications to the public

• **Communicate the risks and benefits of the product through accurate labeling**, i.e. THE LABEL and other directions for use
Drug Development Overview

- **Basic Science**
  - Pre-IND
  - IND 312
  - Ph 1
  - Ph 2
  - Ph 3
  - Ph 4
  - NDA/BLA 314
  - NDA/BLA Review

- **Translational**
  - FDA Interactions
  - Drug Developers and Clinical Investigators

- **Scientific Foundation**
  - undefined

- **Clinical**
  - ~5-10 years

- **Post-marketing**
  - ongoing
Drug Development Tool

- Glossary of terms used for drug development in discussions with FDA


- Posted January 2016, updates Nov 2017
Definitions

• **Biomarker**: defined characteristic measured as part of a biological process

• **Types** of biomarkers: diagnostic, monitoring, predictive, safety

• **Attributes** of biomarkers: validated, surrogate
FDA Definitions [21 CFR 312.3]

• **Sponsor:** individual or entity responsible for and who initiates a clinical investigation. May be an individual or a pharmaceutical company, government agency, academic institution, or other organization.

• **Clinical Investigator:** an individual who actually conducts a clinical investigation. In the event of a team, the investigator is the responsible leader of the team.

• **Sponsor-Investigator:** an individual who both initiates and conducts a clinical investigation and under whose immediate direction the investigational drug is administered or dispensed. (Term does not include any person other than an individual.)
Clinical Research
Who decides if an IND is needed?

- The sponsor (usually sponsor-investigator) of the study is responsible for determining whether an IND is required.
- FDA will communicate with sponsors to assist in determination.
- Contact CDER’s Division of Drug Information (druginfo@fda.hhs.gov) or CBER’s Division of Manufacturer’s Assistance and Training (matt@cber.fda.gov), Office of Communication, Outreach and Development

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm#preIND
Exemption from IND Requirements

21 CFR 312.2(b)

• A clinical investigation of a drug product that is lawfully marketed in the US is exempt if all of the following apply
  – The investigation is not intended to be reported to the FDA as a well controlled study in support of: (commerce items)
    • New indication
    • Significant change in labeling of the product
    • Significant change in the advertising (for prescription drug products)
IND Exemptions-Safety
21 CFR 312.2(b)

Safety Issues:
• The investigation does not involve
  – a new route of administration or
  – dosage level or
  – use in a patient population
that significantly increases the risk with the use of the investigational product

• The investigation complies with:
  – IRB regulations (21 CFR 56)
  – Informed Consent regulations (21 CFR 50)
  – Promotion and charging for investigational drug regulations (21 CFR 312.7)
Is an IND needed?

SAFETY

The hexamethonium asthma study and the death of a normal volunteer (Ellen Roche) in research

*J Med Ethics* 2002;28:3-4 doi:10.1136/jme.28.1.3

http://jme.bmj.com/content/28/1/3.full

Guidance for Clinical Investigators, Sponsors, and IRBs

Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND

September 2013


The study will be conducted under IND

What Now?
• What are the regulations?
• Where do you look for guidance?
Investigator Initiated Studies aka “Sponsor-Investigator”

- Investigator-Initiated Investigational New Drug (IND) Applications webpage
  - Brief explanations about various aspects of IND application submissions and procedures with links to guidances, references, and forms.

Clinical Investigator Responsibilities

CFR 312.60-312.69

- Follow the regulations, signed investigator statement (“1572”), approved protocol and investigational plan
- Protect the rights, safety and welfare of subjects
- Control the investigational drug
- Maintain accurate records and retain records
- Report adverse events to the sponsor
- Report financial disclosure
- Ensure adequate IRB review
Investigator Commitments
Form FDA 1572

- Follow the **current** protocol
- **Personally** conduct or supervise investigation
- Parts 50 and 54 requirements (Subject protection, Informed Consent, IRB oversight)
- **Timely** adverse event reporting to the sponsor
- **Inform** study staff of their obligations
- **Maintain** records
9. COMMITMENTS

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator’s brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.
Information Sheet
Guidance for Sponsors, Clinical Investigators, and IRBs

Frequently Asked Questions – Statement of Investigator
(Form FDA 1572)

May 2010

Form 1572
Clinical Investigator

• Purpose: list individuals who will make a direct and significant contribution to the data

• Depends on level of responsibility in protocol procedures and collection of data

• **Required** updates and changes: new protocol or new CI

• Other changes, sub-I, new IRB do **not** need a new 1572; sponsor can collect changes and submit to IND.
Who should be listed as a Subinvestigator?

- Physicians or other significant study staff
- **Research coordinator** generally has a role in critical study functions: recruitment, collection of study data, maintain study records
- When a non-physician is the CI and medical evaluations are needed
  - E.g. Each subject visits **specific internist** for H&P
Subinvestigator

• Subinvestigator and family are subject to financial disclosure requirements

• Staff that may NOT need to be listed:
  – Hospital Research Pharmacist
  – Providers of ancillary or intermittent care
  – On call physicians who cover occasionally or are involved in the temporary assessment of AEs
  – Ask yourself, what impact do they have on study conduct and data collection?
Guidance for Industry

Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects

October 2009

FDA Expectations for Study Oversight

- Appropriate **Delegation** of study tasks
- Adequate **Training**
- Adequate **Supervision**
- Oversight of **Third Parties**
Practical Advice

• Delegation log
• Documentation of training
• Plans for supervision and oversight-SOPs
• Procedure for timely correction and documentation of problems
• Review of proficiency of staff
• Quality control
Clinical Investigator Recordkeeping and Retention
21 CFR 312.62

• Drug disposition
• Adequate and accurate case histories
• Record retention
  – 2 years following the date of approval of marketing application

Not in regulations: Check sponsor documents-protocol, contract
Clinical Investigator Reports
21 CFR 312.64

• Safety reports-Timely, appropriate
• Financial disclosure-includes family and Subinvestigators
• Progress reports
• Final report
# Sponsors & Contract Research Organizations (CROs) Responsibilities

**[312.50-312.59]**

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Transfer of Obligations to a Contract Research Organization (CRO)

• A sponsor may transfer responsibility for any or all of these obligations to a CRO. Any transfer shall be described in writing.

• A CRO that assumes any obligation of a sponsor shall be subject to the same regulatory action as a sponsor.

21 CFR 312.52
Guidance for Industry

Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

August 2013

Why is monitoring so important?

• Monitoring is a quality control tool for determining whether study activities are being carried out as planned, so that deficiencies can be identified and corrected.

• Effective sponsor monitoring of clinical investigations is critical to the protection of human subjects and the conduct of high-quality studies.
Focus on Conduct and Reporting

• Informed consent
• Eligibility criteria
  – Inclusion-target population
  – Exclusion-safety issues
• Investigational Product accountability and administration
Focus on Conduct and Reporting

• Study Endpoints
• Safety Assessments
• Adverse Events
• Trial Integrity
  – Blinding
  – Adjudication
  – DSMB
Good Clinical Practice (GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Regulation vs. Guidance

required vs. recommended
IND SAFETY REPORTING  21 CFR 312.32
December 2015

Safety Assessment for
IND Safety Reporting
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document, contact (CDER) Dianne Paroan at 301-796-2500 or (CDER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

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)

December 2015
Drug Safety
IND Adverse Event Reporting
21 CFR 312.32

• Serious AND unexpected (not in IB)
  – Death
  – Life-threatening
  – Inpatient hospitalization
  – May require medical or surgical intervention to prevent one of the outcomes above

• SUSAR: Suspected Unexpected SAE
Guidance for Clinical Investigators, Industry, and FDA Staff
Financial Disclosure by Clinical Investigators

February 2013

Financial Disclosure
21 CFR Part 54

54.1 (b) Purpose

FDA may consider clinical studies inadequate and the data inadequate if, among other things, **appropriate steps have not been taken in the design, conduct, reporting, and analysis of the studies to minimize bias**. One potential source of bias in clinical studies is a financial interest of the clinical investigator in the outcome of the study because of the way payment is arranged (e.g., a royalty) or because the investigator has a proprietary interest in the product (e.g., a patent) or because the investigator has an equity interest in the sponsor of the covered study.
Financial Disclosure

• Part 54
• CIs, spouse, dependent children of CIs and subinvestigators
• “Covered clinical study”-can you predict if it will be part of a marketing application?
• What is due diligence?
ClinicalTrials.gov

- **U.S. Public Law 110-85** mandates that a "responsible party" (i.e., the **sponsor or designated principal investigator**) register and report results of certain “applicable clinical trials”
  - Trials of Drugs and Biologics: controlled clinical investigations, **other than Phase 1 investigations**, subject to FDA regulation
  - Trials of Devices: Controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and pediatric postmarket surveillance

http://clinicaltrials.gov/ct2/manage-recs/fdaaa
FDA BIMO Inspection
What is BIMO?

• **On-site inspection** by ORA for compliance, subject protection, data verification

• Bioresearch begun by Francis Kelsey and Alan Lisook (see resource slide) now in CDER, CBER, CDRH

• **Compliance Program Guidance Manuals (CPGM)**
  http://www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/ucm255614.htm
Regulatory Authority to Conduct Inspections/Audits

• 21 CFR 312.68
  – “An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator...”
Inspection Goals and Entities

• Goals
  – Human Subject Protection
  – Data Integrity (PDUFA)
  – Surveillance
  – For Cause to determine violations

• Inspected Entities
  – Clinical Investigator (CI), Sponsor/Monitoring (S/M), Contract Research Organizations (CRO),
  – Institutional Review Boards (IRB),
  – Good Laboratory Practice (GLP), Bioequivalence (BEq) inspection of FDA regulated research.
Process

• Review division in CDER consults OSI for inspections
• OSI writes specific assignment for inspection
• ORA-FDA Field office conducts inspection and submits Establishment Inspection Report to OSI
• OSI reviews EIR and makes determination
Prescription Drug User Fee Act (PDUFA) Related Inspections

Sponsor Submits New Drug Application to FDA

FDA BIMO Inspection

FDA Review Activities

Marketing Approval OR Not
Inspection at CI site

- Can we “re-create” the trial?
- Verification of data submitted to FDA
  Source ➔ CRF ➔ Data submitted to FDA
- Human subject protection: IRB review and Consenting process
- Protocol adherence
- Safety reporting
Inspection at CI site

Source documents: what are they?

– “First put pen to paper”

– ALCOA-accurate, legible, contemporaneous, original, attributable

– Consider: questionnaire, EHR, direct patient data entry via web or PDA

– May be defined in protocol
1.52 Source Documents:
Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).
Inspection at CI site
Recreate the trial

• What type/how were subjects recruited, enrolled and randomized

• Did the study involve blinded and unblinded staff?

• Who had access to treatment assignment and in what situations?
  – Study staff, pharmacist
  – CRO, Sponsor or other third party
What to do if you receive a 483

• Response is advised but there is no regulatory requirement to respond
• FDA requests response within 15 business days
• Include CORRECTIVE ACTION to prevent the finding from occurring again
• “THE MONITOR should have caught it” is NOT an explanation!
Post-Inspection Procedures
OSI Post Inspectional Activities

• Final classification taking into account response from Clinical Investigator
• OSI Recommendation to review division concerning reliability of data
• Additional comments concerning clinical trial conduct
• Post inspectional correspondence (letter) issued to the inspected party
Classifications

• NAI-No action Indicated
  – No objectionable conditions or practices

• VAI-Voluntary Action Indicated
  – Objectionable conditions were found and documented, but the Center is not prepared to take or recommend any further actions

• OAI-Official Action Indicated
  – Serious objectionable conditions warranting action (advisory, administrative, or judicial)
CPGM has Examples

• NAI: following the protocol
• VAI: assessments not completed appropriately
• OAI:
  – assessments not conducted AND the records are falsified to cover this up
  – Repeated or deliberate failure to comply with the regulations
Inspection Results on OSI Homepage

- Clinical Investigator Inspection List (CLIIL)
- Warning letters
- Lists of Disqualified or Restricted or Debarred Investigators
- Metrics

http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm090085.htm
Application-Inspections Overseen by OSI/OSIS*
(CDER, FY 2008 - FY 2017)

*Based on inspection start date – [Complis database as of December 29, 2017]
- Sponsor (GCP) includes Sponsor/CRO/Sponsor-Investigator
- BEQ Application-Inspections accomplished with 289 FY17 Site Visits
- Good Laboratory Practice and Bioequivalence inspection programs operated by OSIS as of January 2015
Clinical Investigator Inspections Classified*
(All Centers, FY 2017)

* CDER, CDRH and CBER numbers based on number of classified inspections reported to BIMO Resource Allocation Metrics PAG for FY17.
• CDER: Center for Drug Evaluation and Research. CBER: Center for Biologics Evaluation and Research. CDRH: Center for Devices and Radiological Health.
Clinical Investigator Inspections by Location* (CDER, FY 2017)

*Based on inspection start date – [Complis database as of December 29, 2017]
Clinical Investigator: Data Audit versus Referral*
(CDER, FY 2017)

* Based on inspection start date – [Complis database as of December 29, 2017]
• Referrals include Complaints, Required Reports, IRB/Sponsor Notifications, and other referrals-internal and external for All OSI Branches
Clinical Investigator Inspections Final Classification*
(CDNER, FY 2017)

*Based on EIR Received date and Final Classification; Includes OAI Untitled Letters, [Complis database as of December 29, 2017]
Frequency of Clinical Investigator-Related Deficiencies Based on Post-Inspection Correspondence Issued*
(CDER, FY 2017)

Domestic CI Deficiencies

- Protocol: 26%
- Records: 15%
- Drug Accountability: 3%
- Consent: 2%
- IRB Communication: 2%
- Adverse Events: 2%

Foreign CI Deficiencies

- Protocol: 18%
- Records: 12%
- Consent: 4%
- Adverse Events: 2%
- Other: 1%
- IRB Communication: 1%

260 Domestic Inspections
121 Foreign Inspections

*Based on EIR Received date and Classification. Inspections may have multiple deficiencies. Includes OAI untitled letters. [Complis database as of December 29, 2017]
Note: this does not denote number of inspections completed, but rather number of inspection reports evaluated and closed.
Clinical Investigator Warning/NIDPOE Letters*
(CDER, FY 2008 - FY 2017)

*Based on letter issue date [Complis database as of December 29, 2017]
NIDPOE = Notice of Initiation of Disqualification Proceedings and Opportunity to Explain
Possible Outcomes of FDA Inspections

• Acceptance or rejection of study data
• Product approval or complete response to sponsor
• Letter or Warning Letter or Enforcement Action (Disqualification Proceedings) for Clinical Investigator
• Results posted on Clinical Investigator Inspection List (CLIIL), updated quarterly
• Education of study site
Possible FDA Actions for Non-Compliance

OAI

- **Clinical Investigators:** Warning Letters
  NIDPOE Letters
  Disqualification
  Debarment (Office of Enforcement)

- **Sponsors/CROs:** Warning Letters and Rejection of data
  Clinical Holds or Termination of IND
  Application Integrity Policy

- **IRBs:** Administrative actions or Disqualification

- **Possible Referral to Office of Criminal Investigations (OCI)**
Take Home Messages

Address the human factors in your system

- Hire experienced, qualified staff and provide adequate training
- Avoid conflicts of interest/financial incentives
- Decrease number of times data are handled
- Be realistic about ability to comply with protocol visits and assessments; electronic systems for data capture, archiving and transmission; maintaining records, drug accountability
Process Improvement

Create systems that limit opportunity for errors

- Be realistic about the amount of data to be collected
- Standardize systems and formats where possible
- Use SOPs and checklists
- Don’t re-invent the wheel
- For Protocol amendments check the CRFs and consent form against each change
- **Be honest** and evaluate need for system wide corrections and training
Summary

• QUALITY “built into” a clinical trial with appropriate protocol and SOPs
• Adequate Resources and Culture of Excellence are important components
• Continuous assessment of procedures to IDENTIFY and FIX problems
• Adherence to the REGULATIONS is REQUIRED
• GUIDANCES available for ADVICE
Contact Information

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Thank you!
Office of Scientific Investigations

• OSI and History of FDA’s BIMO program
  http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm091393.htm#history

• Clinical Investigator Inspection List (CLIIL) results going back to 1977
  http://www.fda.gov/Drugs/InformationOnDrugs/ucm135198.htm
OSI History of First GCP Inspection

CPGM and CFR: Links

• Basics for Industry: What should I expect during and Inspection?
  http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm237624.htm

• CPGM: manual of instruction inspections and guidance for ORA investigators
  http://www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/ucm255614.htm

• Code of Federal Regulations
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm
Guidance Documents

• Clinical Trials Guidance documents
  http://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm

• Investigator Responsibilities: October 2009
Information Sheets and FAQs

- FDA Inspections of Clinical Investigators- Information sheet June 2010

- Frequently Asked Questions – Statement of Investigator (Form FDA 1572)
Where else to go?

- Regulatory Affairs at your Institution
- Organizations: **SoCRA**-see link at FDA website above and **CITTI** at [http://ctti-clinicaltrials.org/home](http://ctti-clinicaltrials.org/home)
OGCP links

• **OGCP Contacts and Mailbox**
  
  http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm134476.htm

• **Archived replies**
  
  http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/RepliestoInquiriestoFDAonGoodClinicalPractice/default.htm

• **Searchable archives**

• **http://www.firstclinical.com/fda-gcp/**
Small Business and Large Industry

• FDA Basics for Industry
  • http://www.fda.gov/ForIndustry/FDABasicsforIndustry/default.htm

• Small Government Assistance
Drug Development

• When is an IND needed?
http://www.fda.gov/forindustry/fdabasicsforindustry/ucm237990.htm

• Drug Development and Approval Process