Documenting the Story of a Clinical Trial: Concept to CAPA

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“The regulations represent the floor while ethical thinking is the sky.”

Dr. Thomas Moore

Boston University School of Medicine

Associate Provost


Once upon a time...

What Am I?
(And what are they?)

Sponsor

Collaborator

Investigator

Investigator-Sponsor

Sponsor

A person who takes responsibility for and initiates a clinical investigation. . . **may be an individual or company, government agency, academic institution, private organization, or other organization**. . .

21 CFR 312.3

✓ COLLABORATOR

- Financial Support
- Protocol Development Assistance
- Provision of Product
- Anything other than a contractual statement and/or listing on the form 1571 designating “Sponsor”

Investigator

An individual who **actually** conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject).

21 CFR 312.3

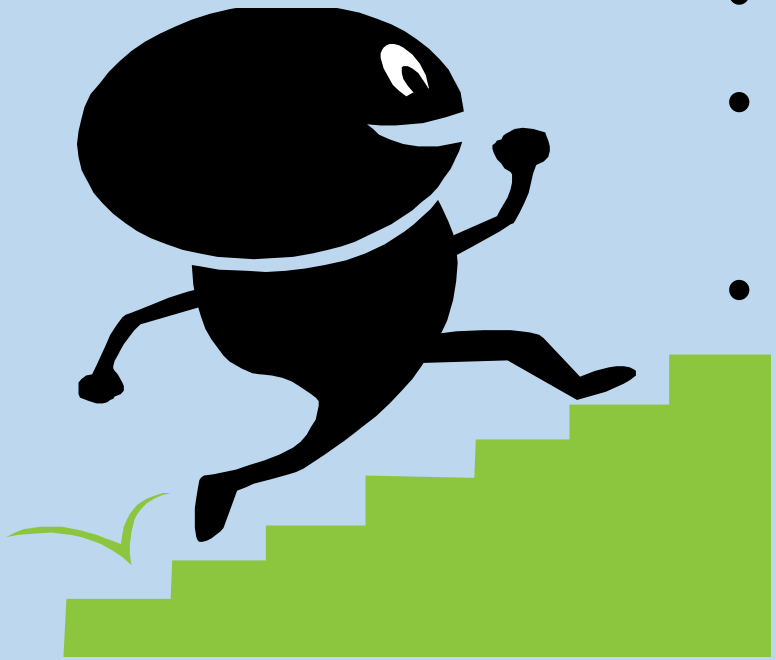
Sponsor-Investigator

Individual who both initiates & conducts a clinical investigation, and under whose immediate direction the investigational drug is administered or dispensed.

The term does not include any person other than an individual. The **requirements applicable to a sponsor investigator under this part include both those applicable to an investigator and a sponsor**.

21 CFR 312.3

Levels of Accountability



- Federal Regulation / Guidelines
- Global Guidelines (ICH GCP)
- State Regulations
- Institutional Requirements
- Contractual Agreements (Sponsor/CRO)
- Practice Standards (SOPs)

Federal Regulation and ICH E6

Law

vs.

Guidance

Essential Documents

"8.1 GCP: Essential Documents are those documents that individually and collectively permit **evaluation** of the **conduct of a trial** and the **quality of the data produced**. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements."

What are the documents that can be mandated an essential document?

ANYTHING…….

requested by one of the authorities you are accountable to

The First Chapter……..The Protocol

- Rationale for study
- Clear measurable objectives
- Identifies study population (inclusion/exclusion)
- Clear and precise methods/processes
- Statistical Analysis Plan
- Identification of safety concerns
- Data and Safety Monitoring Plan
- Informed Consent/HIPAA Template

The Prequel

What does success look like?

- Define site approval criteria
- IMPORTANT: A site saying “yes” is not the deciding factor

Essential Documents

ICH E6 Consolidated Guidance, Section 8

I. Pre-Trial Phase

II. During Conduct of Trial Phase

III. Post-Trial Phase

IV. Other

Executed NDA

The Casting Call…….

- CV/Lic.
- GCP, HSP, HIPAA, etc. training
- Not on FDA Disbarment Lists
- Miscellaneous attributes

Finding the location…..

Clinical practice diversity

Demographic subject diversity

Geographical Diversity

More than just a pretty name……..
Infrastructure Assessment

- # of studies / competing studies
- # of qualifying subjects (for real)
- Dedicated study team personnel?
- Ability to perform procedure (SOC vs. alternative)

- Adequate equipment / access to dry ice?
- Adequate space, security, and access
- Appropriate certifications of labs
- SOPs for required processes
- Assessment of medical records/ Part 11 compliance

Other nice to know info……..

Contracting:

- Separate from budgeting?
- Contacts/signatory
- Overhead?
- Turn around time

IRB's:

- Central vs. Local
- # of panels
- Meeting schedule
- Lead and Review time
- Other committees?

Tag, your it!.....The second wave of documents

- Contractual Agreement
- 1572 or Investigator Agreement
- Financial Disclosures
- Protocol signature page
- Investigator Brochure receipt

Financial Disclosures

- Required of all clinical investigators who treat, evaluate research subjects or make a significant contribution to the research data.
- Includes the investigator, spouse, and dependent children
- Disclose equity interest of >$50K/ or other payments of >$25K
- Disclosure updates required until 1 year after completion of study.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: March 31, 2019

TO BE COMPLETED BY APPLICANT

The following information concerning _____ , who participated
Name of clinical investigator

as a clinical investigator in the submitted study _____
Name of

_____ is submitted in accordance with 21 CFR part 54. The
clinical study

named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable check boxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
FIRM/ORGANIZATION	
SIGNATURE	Date *(mm/dd/yyyy)*

This section applies only to the requirements of the Paperwork Reduction Act of 1995.

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PSC Publishing Services (301) 443-6740 EF

Signed Investigator Statement (1572)

- Provides the “demographics” of the study
- Commitment to compliance (investigator and staff)
  - Protocol
  - Regulation
  - Human Subject Protection

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.

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Local approvals…..The IRB, SRB, etc.

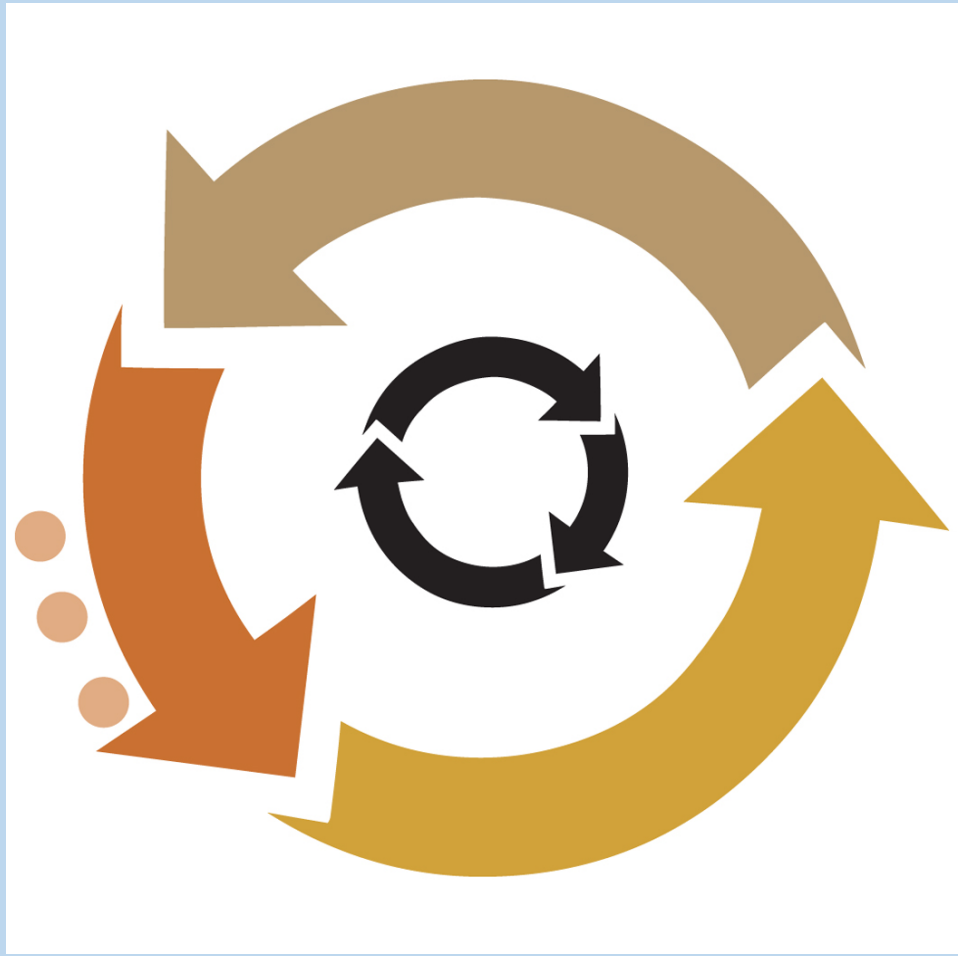
- If multiple reviews, know the order
- Submit all applicable materials
  - Protocol
  - Team members
  - Information for subjects
  - Advertisements
  - CRFs

- Collect IRB roster or FWA assurance letter

And the curtain rises…….Site Initiation!

- Site Initiation Visit Report
- Delegation of Authority/ Site Authorization log
- Material Receipts
- Material Accountability
- Temperature Logs
- Protocol training
- Possible eCRF training
- Collection of any outstanding documents

Control and Accountability of Investigational Drug or Device



The plot thickens……

- Interim Monitoring visit report / follow up letters
- Any amendments or updates to Protocol, IRB updates/reports; or updates to Reg Docs already collected
- Relevant Communications
- Screening /enrollment logs (and code lists)
- Signed ICFs/HIPAA forms
- Screening /enrollment logs (and code lists)
- Completed, Signed and dated CRFs
- Queries
- Adverse Events
- Deviations
- Notes to file
- Sample retention documents
- Site visit logs
- Source Docs

The FDA's "ALCOA" requirement for source documentation

- **Attributable**: is it obvious who recorded it?
- **Legible**: can it be read?
- **Contemporaneous**: is the information in the correct time frame (how much time elapsed from the time of observation to the time of recording)?
- **Original**: is it a copy; has it been altered?
- **Accurate**: are conflicting data recorded elsewhere?

The Closing Curtain……

- The Close out visit
- Disposition of Investigational Materials
- PI Summary (compilation of enrollment, AEs, Deviations, issues, did everything go as planned?)
- Close out report to the IRB (only after sponsor authorizes)
- When applicable decoding documentation
- Any reports to granting institutions
- Audit certifications (if applicable)

Appropriate recordkeeping and record retention (§ 312.57)

- Retain records/reports pertaining to part 312
- All financial interests to investigators
- Documentation of test article: to whom shipped; where; when; quantity; batch code
- Reserve test articles and reference samples

2 years after last shipping of IND product; or 2 years after approval

But wait, there’s more……

CAPA

Corrective And Preventative Action

CAPA: 21 CFR 820.100 requires a manufacturer to:

- Establish and maintain CAPA procedures
- Analyze all sources of quality data to identify causes of quality problems
- Investigate the cause of nonconformities
- Identify actions needed to correct and/or prevent quality problems
- Implement the solution
- Verify or validate the actions taken as a solution
- Ensure information about the problem and changes is disseminated within your organization
- Submit relevant information about CAPA activity for Management Review
- Make sure all CAPA activity is documented

Responses to Audit/Assessments:

- Responses to 483 observations from FDA audit
- Responses to IRB audit/assessments
- Responses to Sponsor Audits or monitoring
- Responses to Grantor Audits or assessments
- Responses to other Institutional Audits or assessments (Data Management; Quality; etc.)

Formulating a Plan

- Issue is identified
- Root Cause Analysis (Why?)
- Correction
- Corrective Action
- Preventative Action
- Evaluation

Providing Effective Responses

- Clear/Concise
- Measurable/Evaluable
- Intervention appropriate for issue

Site Corective Action Plan

Protocol ID: Sponsor:

Site #/PI Name: Notification to:

CAP initiation Date: Notification date:

Date of Issue Identification	Issue	Corrective Action	Planned Date of Resolution	Responsible Person(s)	Investigator Initials & Date	Actual Date of Resolution

Date:
To:
From:

The following CAP is in response to the observations noted by [fill in name of auditor/agency] identified on [fill in date].

Issue: Brief description [include all details: event/issue; when it occurred; when it was originally identified; by whom if applicable]

Root Cause: The reasons that the issue arose [This should be a concise narrative of the findings of your investigation/assessment of the issue]

Correction: What was done to correct/or respond to this specific issue [did the subject require treatment; was and AE or Deviation filed and reported to the IRB; was the data removed from analysis; was further documentation obtained; etc]. When applicable, give names of personnel completing the action and when the action occurred.

Corrective Action: What action was taken to correct the cause of the issue [for example: did the protocol need to be amended; was a process changed; was training required]

Preventative Action: (Note: only applicable to issues identified as potential risks)

Effective date of resolution: Actual date of resolution

Evaluation / Follow up: Was there, or is there a plan for a follow up assessment to insure that the issue does not re-occur (if so, plan may need to be revised).

Comments:

_____ _____

Principal Investigator Signature Date of Signature

_____

Principal Investigator Printed Name

And they lived happily ever after!