Managing Study Compliance: A Site Perspective

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Disclosure

I have no relevant financial relationship in relation to this educational activity.

Learning Objectives

Upon completion of this presentation, participants should be able to:

- Examine sponsor, institution and Investigator regulatory requirements.
- Describe practical suggestions to improve site compliance
- Identify factors that may contribute to non compliance
- Propose methods to facilitate compliance

Question!

- What is GCP?

Something to think about!

- Know GCP = Compliance
- No GCP ≠ Compliance

BIMO

- FDA Bioresearch Monitoring Program

Why Compliance Matters

- Assurance of data quality and human subject protection in clinical studies
- Assurance that the conduct of the investigation meets acceptable standards and guidelines
- Real world implications for investigational products

Sponsor Requirements

- FDA IND and IDE regulations obligate sponsors to oversee their clinical trials
- 21 CFR 312.50 and 812.40: Sponsors are responsible for ensuring proper monitoring of the investigation
- ICH guidelines E6 (R2) Section 5.18
- Requirement that sponsors verify:
  - Rights and well being of human subjects are protected
  - Clinical trial data are accurate, complete and verifiable from source documents
  - Conduct of the trial is in compliance with the currently approved protocol, amendments, GCP and regulatory requirements.
- Other training requirements

Investigator Requirements

- Requirements of the Principal Investigator (drugs, biologicals, devices):
  - Study conducted according to the signed investigator statement (includes adequate supervision)
  - Rights and well being of human subjects are protected
  - Control of the drug, biological or device under investigation
  - Clinical trial data are accurate, complete and verifiable from source documents
  - Conduct of the trial is in compliance with the currently approved protocol, amendments, GCP and regulatory requirements.

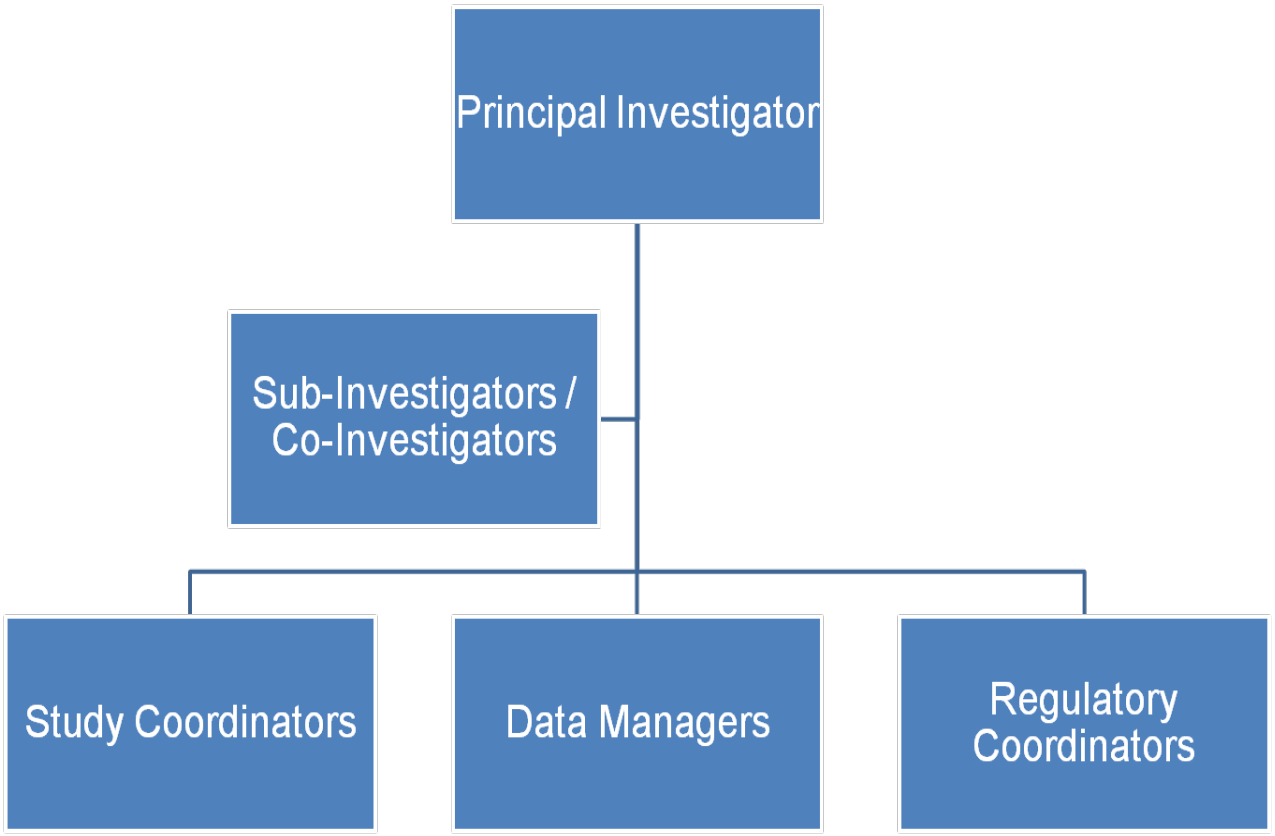
Institutional Requirements

- Federalwide Assurance (FWA)
- Good Clinical Practice (GCP)
- Human Subjects Protection – CITI/NIH
- Conflict of Interest
- HIPAA
- Dry Ice Shipping/IATA
- Blood Borne Pathogens
- Laboratory Safety

Protocol Level Requirements

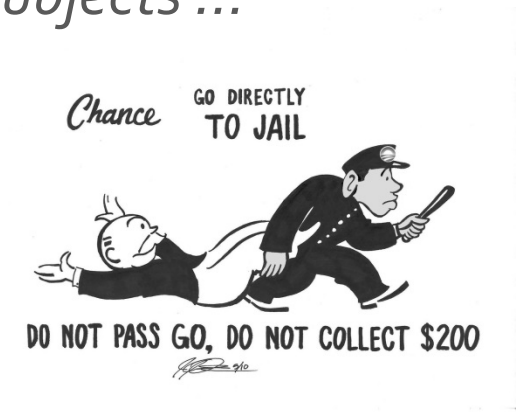
- Protocol specific training
  - Lab handling/processing
  - Drug/Device storage, dispensing, handling
- Sponsor specific training
  - Medical events of special interest
  - Study specific technology
- eCRF data capture systems
- Other

Research Team



Words to Avoid…

"You failed to personally conduct or supervise the clinical investigation … your lack of supervision resulted in significant findings as detailed below, and raises significant concerns with respect to data integrity and how you protected rights, safety and welfare of study subjects …"



Informed Consent Process

- Monitors, auditors and FDA inspectors will confirm that the informed consent process has been performed properly.
  - Correct consent (or assent)
  - Correct version
  - Proper signature and date by the participant, person obtaining consent and PI (if applicable)
  - No study related practices carried out prior to consent

Barriers to Compliance

- Lack of knowledge/education
- Human error
- Hidden non-compliance
  - Consent practices

Informed Consent Documentation

Name of the Note: Clinical Research Progress Note

Clinical Study: INFORM Study (IRB 16- 12345)

Visit / Day: Screening visit

Mr. Bond presented to the Premier Research Center alone for consideration of the aforementioned trial for adults with {Condition}. Participant and the research coordinator reviewed the consent form and the purpose of the HIPAA consent. The consent form was previously mailed to the patient for review prior to the study visit. The procedures for the study (Phase 1 vs Phase 2) were reviewed and included, but was not limited to, the purpose of the study, study procedures, duration, potential risks and benefits of the study and the right to withdraw at any time.

Patient questions included whether he would receive payment during the study and how long his participation in the study will be. All questions were answered to the satisfaction of the patient. He expressed willingness to participate and verbalized understanding of the components of the study as documented. Participant signed the consent form(s) in the presence of the study coordinator. A signed and dated copy of the consent form and HIPAA ICD was provided to the pt for his records. No study related activities were conducted prior to signing consent. Study I/E criteria also reviewed with the patient.

Vitals -
Weight: obtained as per protocol
Blood Pressure (after sitting 5 minutes): obtained as per protocol

Labs -
Local blood samples (CBC, ALT, Serum Creatinine) were obtained as required for screening. Pt reminded that study labs at final run-in visit would determine ultimate eligibility for the study.

Medical History -
Obtained by treating physician as documented in EMR

Conmeds -
Reviewed and verified with the patient from EPIC and interview. Participant denies taking Aspirin in the past 6 months.

RTC: pending screening labs for continuation of the study.

Signature/Date

_____

Informed Consent Documentation

INFORMED CONSENT & RECONSENT DISCUSSION CHECKLIST

Clinical Research Trial: _____ **Patient:** _____

Protocol Version Date: _____ **Amendment:** _____

YES	N/A	
		Physician discussed diagnosis and treatment options (standard of care, no treatment)
		Physician discussed clinical research trial including the following:
		• Description of the clinical research trial, its goals, and medications involved
		• Voluntary participation
		• Anticipated duration of participation
		• All known risks: reported side effects and management of known side effects and • Possibility of unknown side effects
		• Potential and reasonable expected benefits
		• Treatment groups and randomization (if applicable)
		• Required study procedures
		• Optional correlative biology procedures (if applicable)
		• Follow-up after completion of study treatment
		• Rights and responsibilities of research participants
		• Risks to unborn child(ren) and contraception discussed (if applicable)
		• Confidentiality
		• Compensation / Additional costs
		Consent presented to patient / legal representative / legal guardian
		Time allowed for patient / legal representative / legal guardian to read consent and ask questions prior to signing consent
		Patient / legal representative / legal guardian acknowledged understanding of the clinical trial and indicated questions were answered to their satisfaction
		Patient / legal representative / legal guardian signed informed consent
		Patient / legal representative / legal guardian received a copy of each signed research consent form
		Study specific procedures were not done prior to consent being signed
		Contact information provided to patient / legal representative / legal guardian for study related concerns

Consent document(s) signed on _____/_____/_____ Time consent signed: _____ AM PM

**Translation Services: Translated document(s) and / or interpreter provided as needed:

NO (translation services not needed) YES List language provided: _____

Any additional comments regarding translation: _____

Name of MD or NP obtaining consent (print): _____

Signature of MD or NP obtaining consent: _____ Date: _____

Confirming Subject Eligibility

- Request medical records for confirmation
  - Request original imaging, pathology, labs etc…
- Patient can lie, forget or don't think some information is relevant.
- Data for each line of I/E
- Labs, clinic notes, procedure notes etc. that confirm eligibility

Confirming Subject Eligibility

- Some data may need to rely on the word of the participant. Requires proper documentation
  - Known HIV status
- Some items may be currently unknown
  - Allergy to Chinese hamster ovaries

Barriers to Compliance

- Not interpreting the protocol literally
- Lack of supporting source documentation
- Missed assessments to establish eligibility
- Misinterpreting lab results (ULNs)
- Poorly worded criteria
  - "Poorly controlled diabetes"
  - "Uncontrolled Hypertension"

Study Management

- Familiarity with time and event table and protocol contents
- Effective communication with staff involved in the care of the participant
  - Inpatient vs Outpatient
- Proper documentation of deviations
  - Pre-approval of planned deviations
  - Are documented deviations truly deviations?
  - Sponsor approved protocol deviations

Study Management

- Creation of Source documentation
- E.g.: CRF asks for smoking history and caffeine intake
  - Standardized source templates: checklists, medical history, physical exam, research notes
- Clinical note vs. Research note
  - Tells the story of what occurred during the visit
- Avoid/Reconcile duplication of recorded data
  - Clinic notes, vital signs etc.

Sample Research Note

Name of the Note: Clinical Research Progress Note
Clinical Study: INFORM Study (IRB 16-1234)
Visit / Day: 6 Month Visit

A, BC presented to the Premier Research Clinic with her sister for continuation on the aforementioned trial for adults with {Condition} on {Drug}. The following occurred, were reviewed or discussed during the visit.

Vitals -
Weight/Height: obtained as per protocol
T/P/BP/R: obtained

Local Laboratory Assessment -
Local blood samples (Hematology & Chemistry labs) were obtained as required for this visit.
Patient reports fasting, NPO since at least midnight the night before.

Adverse Events –
Patient reports no nausea, vomiting, headaches, fatigue or other symptoms. She states that she is doing well since the last visit. Patient did mention having a small raised area on her left forearm. She states it is does not hurt, or itch. It is slightly red and was noticed about two weeks ago. Provider assessed during the visit and will monitor. Encouraged to call with questions if it worsens.

Patient continues wearing braces at this visit. These were placed on 21JUL2015.

Conmeds -
Reviewed by the provider and coordinator with the patientt. Participant denies starting or stopping new medications since the previous visit. Continues Tylenol as need for menstrual pain.

Diaries/QoLs –
Diary reviewed. Copied and returned to the patient. Noticed in retrospect that times for evening meal were not recorded, will emphasize the importance of diary completion at the next visit.

Drug dosing –
Due to change in weight, dosage increased from 350mg PO BID to 400mg PO BID starting today. Patient reports missing one dose of study drug as noted on diary.

Drug Dispensing –
Dispensed:
3 bottles (200mg bottles)
Returned:
3 bottles; 1 full bottle; 2 bottle - multiple capsules remaining

RTC: Month 9 Visit
Signature/Date

_____

Barriers to Compliance (Site)

- Lack of knowledge/understanding of the protocol
  - Time and events table
  - Protocol text
  - Missed assessments
- Checklists
  - Required assessments/study process
- Inpatient vs outpatient design
- Logistics at the site

Barriers to Compliance (Patient)

- Inadequate patient education
  - Expectations
  - Informed consent process
  - Little emphasis on importance of QoLs/Diaries
  - Improper use of investigational drug or device
  - "Hassle factor"
- Think outside the box

Completion of CRFs

- Art of data entry
- Goals
  - Timely
  - Accuracy
  - Query reduction
  - Ensure data are entered per the sponsor's specifications (eCRF guidelines)
- Learn to anticipate what could be a questionable entry leading to queries

Completion of CRFs

- Repeated blood pressure due to elevation
  - Which value is entered?
- Patient diary indicates 1 dose was missed, but the bottle has no pills remaining
  - Which value is entered?
- Medical record says pt was diagnosed with diabetes in 1996, pt says was 1992
  - Which year is entered?

Barriers to Compliance

- Timeliness of entry
  - Missed opportunities to catch errors
- Missing data
- No data entry guidelines (or non use)
  - Should not conflict with the protocol
- Lack of attention to detail
  - Entering relevant data
    - Medications, medical history
    - All adverse events vs ≥Gr3 events
    - Specific terminology for coding purposes

Managing AEs, SAEs, UPs

- Medically qualified staff on the study make attribution of causality to the investigational product (MD, NP, PA)
- SAEs/MESIs reported within 24 hours of site knowledge
  - Reporting criteria clearly defined in the protocol?
  - Any admission?
  - Admission >24 hours?
  - Observation?
- AEs may not be immediately reportable to IRB

Regulatory

- Delegation of Authority log maintenance
- Protocol training for staff on delegation log
  - Variety of methods to capture training
    - Review study at weekly staff meetings
    - Individual review of protocol or SIV slides
    - Learning Management System
  - Standard form to document training
- Timely submission of protocol amendments
- Trending: Electronic regulatory files

Barriers to Compliance

- Lack of familiarity with GCP and requirements for regulatory document management
  - Subsequent training and documentation of protocol changes
- Timely review of ICF/IAFs for submission
- Opening studies quickly
  - Documents can be overlooked
- Site work flow/dynamics that impact submission of amendments, administrative letters, annual reports etc.

Monitoring Letters

- Summary of the visit and trial management
- Read the letter
- Discrepancies?
  - Speak with the Monitor to clarify
  - Is an amendment possible?
  - Note to file in study files
- Some IRBs require submission at study renewal.

Barriers to Site Compliance

- Lack of PI oversight
- High staff turnover
- Inexperienced or poorly trained site staff
- Lack of understanding about the regulations
- Management of multiple studies
- Competing priorities

Can apply to the site and the sponsor

Sponsor Support & Compliance

- Protocol
  - Simple protocol, complicated study
  - Hidden requirements (100% SDV & source submission) – does not allow for adequate planning
- Informed Consent Documentation
  - Reminder: GCP requirement
- Eligibility Criteria
  - Sponsor provided checklists (should agree with the protocol)
  - Well defined criteria to reduce ambiguity

Sponsor Support & Compliance

- Protocol Management
  - Newsletters
  - Templates for source documentation
  - Connect with high performing sites
- Completion of Case Report Forms (CRFs)
  - Availability of CRFs prior to study start-up
  - Data entry guidelines
  - Tips for query reduction

Cartoon by Amanda Plante and Tim Brown

Communication

- Opportunities for synergy
  - def: the interaction of elements that when combined produce a total effect that is greater that the sum of the individual elements
- Opportunities for education and support
  - GCP vs. sponsor SOP vs. personal preference
- Common goal and objective
- Resource to support compliance
- Dispel the myth…

Final Thoughts

Suggestions:

Adapted from: https://biostatinternational.com/blog-inside-bsi/

- Be the point person for the study protocol; find out relevant information and relay back to the site
- Communications: find out the best method for your coordinator - a second email, a phone call or texting and the best times are to call. Also note the typical at-the-work desk times
- *Understand* the work flow process for the department, who does what tasks
- Find out how the patient flows through the hospital/clinic system

Final Thoughts

- Be aware of the site's local events, news, weather, etc., these are good conversation starters and help build relationships
- Come with an approachable, let's work together attitude. Be patient, not all action items can be dealt with in single visit
- Avoid being judgmental and overly critical. Most errors and deviations are innocent. Plan to address using CAPA principles - learning experience for the site
- Be aware of the atmosphere at the site for subtle clues in body language and emotions that might help adjust the agenda for a more productive visit

Final Thoughts

- While reviewing the records, write down or flag items to discuss at the end of the visit as part of de-briefing; this is part of the study protocol reinforcement process
- Monitors make mistakes too, be willing to correct errors
- Be aware of the big picture; there may be opportunities to work with the site again, so it is important to be a good ambassador for clinical research

References

- Guidance for Industry; Investigator Responsibilities—Protecting the Rights, Safety, and Welfare of Study Subjects October 2009 https://www.fda.gov/media/77765/download
- Ensuring the Safety of Clinical Trials (Investigations). http://www.fda.gov/downloads/Training/ClinicalInvestigatorTrainingCourse/UCM378800.pdf
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Something to think about!

- Know GCP = Compliance
- No GCP ≠ Compliance

Questions

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