2009 Necessary Elements in the Fundamentals of
Human Subjects Research: Investigator Initiated
Studies for the Study Coordinator

Conferences

2009

Now . . . what do I do with all this paper

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http://digitalcommons.wustl.edu/hrpoconf_subres2009/4

Now.....
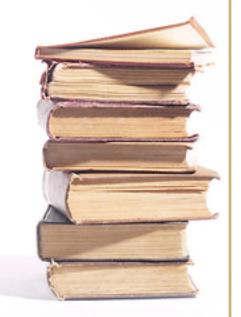# What Do I Do With All This Paper

Michelle Jenkerson

Research Participant Advocate

Washington University School of Medicine

Now We Know….

- How to write a protocol – Dr. Kharasch

- Grant vs. Protocol – Dr. Coopersmith

- Protocol Issues – Sarah Fowler-Dixon

- Now we need what to do with all this.........

Objectives

- Familiar with research data to capture

- Essential regulations

- Organizing research records
  - Regulatory binder
  - Participant research records

- Understanding what "research data" is
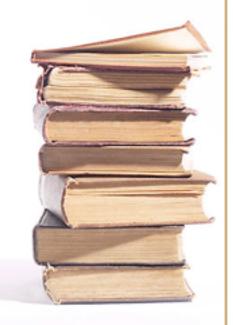
- Knowing what a source document is

Read & Re-Read

- Become familiar with the protocol
  - Take notes
  - Highlight
  - Place sticky notes
  - Look at logistics
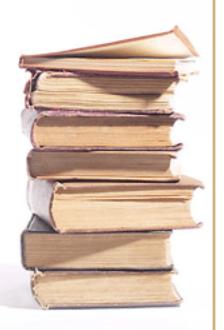- Now that you are familiar we can proceed

Consider Writing Standard Operating Procedures (SOPs)

- Purpose:
  - Ensure consistent processes
  - Meet or exceed regulatory & GCP standards

- Ensure processes are reviewed & updated on regular basis

SOPs – Not Required by Regulations

- 21CFR 312.53:
  - "The PI will ensure that all staff are informed about their obligations."

- SOPs:
  - Better prepares study team

  - Processes will be consistent

  - Appear more professional

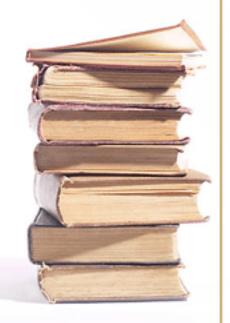 - FYI: Industry are now asking to review SOPs

SOPs
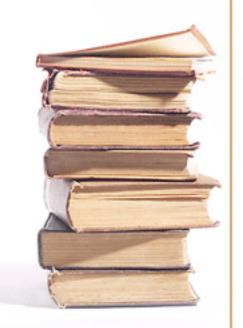
- Writing SOPs

  – Not easy task

  – Time consuming

  – Analysis of processes

SOPs vs. Guidelines

- SOP:
  - Gives a birds eye view of process
  - Include all the main steps
- Guidelines:
  - More detailed
  - Allow someone to complete the process by following steps in guideline
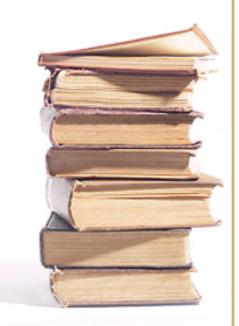
SOPs vs. Guidelines

- SOPs:
  - Approved at higher administrative level
  - Not changed on a whim
  - Rarely need to be changed
- Guidelines:
  - May change more frequently
    - Changes:
      - Organizational structure
      - Equipment
      - Personnel functions
    - Formulated or updated at departmental level

SOPs vs. Guidelines

- More than 1 guideline attached to an SOP

- Some SOPs may not need guidelines
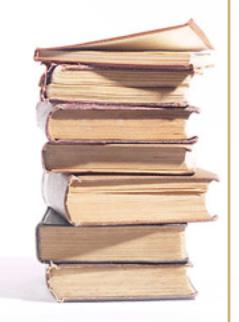
SOPs vs. Guidelines

- SOPs Sections:
  - Header
  - Scope
  - Purpose
  - Procedure
  - Attachments
  - Applicable Regulations, Guidelines, Resources, References

- Guidelines:
  - List tasks to complete process
  - List person or function responsible for completing each task
  - Much more detailed
    - May need to be changed, even if SOP remains valid & appropriate

SOP & Guideline Approval Process

- SOPs
  - Subject to review by any groups or departments that are affected by them

  - Review helps ensure that processes can & should be followed

SOPs

- Recommendation:
  - Review annually or every 2 years
    - Ensure they are still workable
    - Ensure they are being followed
  - Changes:
    - SOPs should be revised to reflect change
    - Amend guidelines
  - Assign someone to maintain SOPs/Guidelines:
    - Current
    - History of documents & revisions
    - Maintain all previous versions – include dates during which SOP was in effect
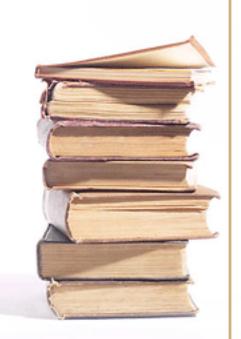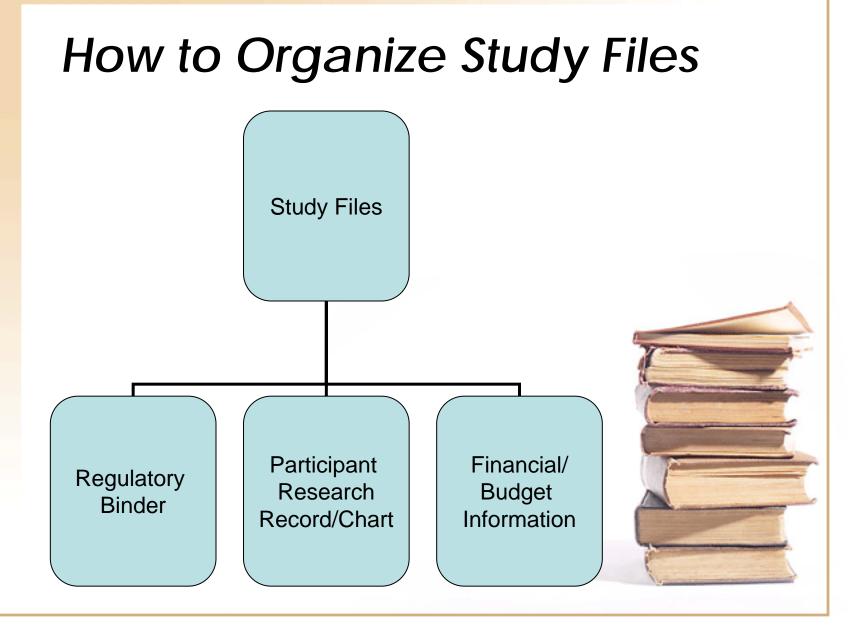   - Provides an audit trail for process changes

Approved SOPs & Guidelines

- Critical:
  - Train personnel involved
  - Only functional if people know what they are & follow them
- Approved:
  - Train staff
  - Implement
  - Note: approval date usually precedes the implementation date
  - Employees should have access
    - Online
    - Hard copies

What Do We Do With All These Study Related Papers??

How to Organize Study Files

Study Files

Regulatory Binder

Participant Research Record/Chart

Financial/ Budget Information

Always Remember

- Documentation of research data is not optional.....<u>it is a must!</u>

- Complete record keeping = valid data integrity......<u>it is a must!</u>

- Keeping essential "research information" is the law.......<u>it is a must!</u>

- Complete & proper documentation & record keeping is an "ethical" practice.....<u>it is a must!</u>

- Incomplete data & record keeping:
  - Potentially may keep data from being published

Who Is the "Sponsor"

- Note:
  - In Investigator-initiated studies, the PI as the Investigator may hold the IND and also have all the sponsor responsibilities

  - The sponsor of a study (to whom the IND is issued) has extensive obligation under 21 CFR 314 (e.g. study monitoring, adverse event and other reporting to the FDA)
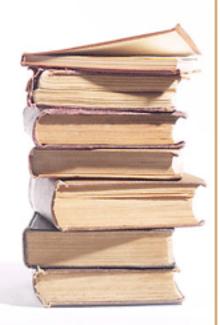
Creating Files- Regulatory Binder

- Protocol
- Grant & updates
- IB, if applicable
- 1572, if applicable
- 1571, if PI is IND Sponsor
- CVs of PI and Sub-Is
- Licenses
- Training Certificates,
  - HIPAA
  - CITI
  - Signature Logs
- Other Credentials, if appropriate
- Clinical Investigator Financial Disclosure Forms
- Drug Data Sheets
- Letter HRPO membership & Assurance #
- SOPs – for this protocol
- Emergency Un-blinding procedure, if applicable

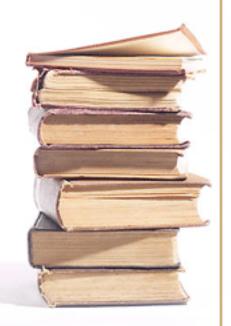# *Creating Files- Regulatory Binder, Continued*

- HRPO Correspondence
  - Initial Approval
  - Consent forms
  - Amendments
  - AE/SAE reports
  - Advertisement
  - Continuing Renewals
- DSMB Reports
- Normal lab values & tests that will be used
- CLIA/CAP certification for lab – if required
- Delegation of Authority Log/Staff signature log & initial log
- Sponsor Correspondence, if applicable
- FDA Correspondence, if applicable
- Study Agreements
- Contracts
  - Disclosure Agreements
  - Other sites, if applicable
- Samples
  - Data collection forms –Source Docs
  - CRFs
- As study proceeds, may need to file external adverse event reports and IND safety reports

An Old Nursing Adage:

Repeat after me:

"If it's not documented, it wasn't done."

Definition: Participant Research Record/Chart

- Often, a separate research record maintained in addition to the patient medical record, - research purposes
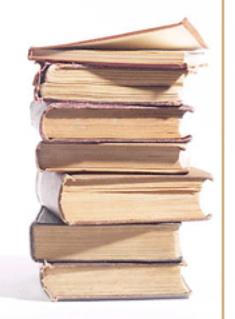
PI Responsibility

- FDA 21 CFR 312.62 (b)
- Investigator record keeping & record retention:
  - "Case histories: An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation."

21 CFR 312.62(b)Continued:

- "Case histories include the case report forms and supporting data including, for example, progress notes of the physician, the individuals hospital chart(s) and the nurses' notes. The case history for each individual shall document that IC was obtained prior to participation in the study."

Participant Research Record

- Consider how:
  - Organize record/chart

  - Participant's will be identified:

    - Unique identifier –Master List

    - Number – Master List

    - Initials plus number – Master List
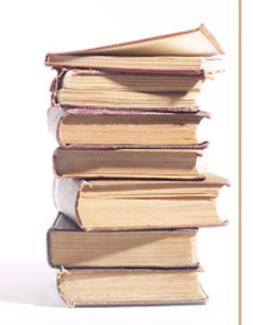
    - By Name

Also Prepare

- Maintain a screening log:
  - Date screened
  - Date randomized
  - If kept on computer
    - password protect

- Maintain enrollment Log
  - Date of enrollment
  - If kept on computer
    - password protect

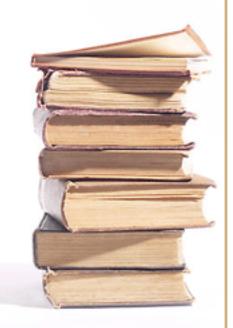# *Contents of Participant Research Record*

- Signed & dated IC
  - Original – no copy
- Short narrative:
  - Consent process
  - Copy of IC given to participant (ICH E6 4.8.11)
    - "A copy of the ICD must be provided to the subject & the original signed ICD should be retained in the study records" Note, FDA regulations do not require the subject's copy to be a signed copy, although a photocopy with signatures is preferred. (FDA Information Sheet 1998 Update)

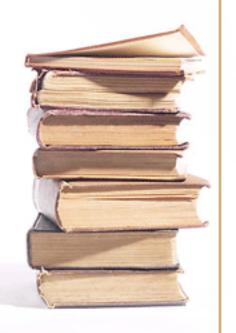# *File Supporting Documents In Participant Research Record/Chart*

- I/E criteria reviewed

  - Met inclusion
  - Met no exclusion

    - Check-off list
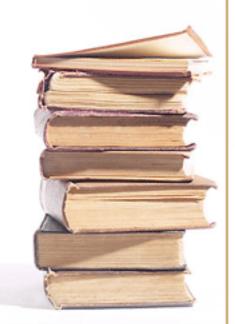   - PI review – sign & date

Creating Participant Research Record/Chart

- Set up per visit schedule
- Forms
  - Actual research data that supports the data recorded or measured
  - (Can only collect data per protocol)
- Know data to collect for each visit
- Need to validate data:
  - Comes from source docs
  - Source docs must be available to review
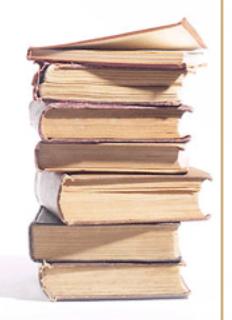- Organize & file....asap

Source Docs Can Be:

- Original docs
- H & Ps (eligibility)
- Data
- Records
  - Hospital
  - Clinical
  - Office
- Lab notes
- Memoranda
- Diaries
- Evaluation checklist
- Pharmacy dispensing records
- Recorded data from automated instruments
- Copies or transcriptions certified after verification as being accurate copies
- Microfiches
- Photographic negatives
- Microfilm or magnetic media
- X-rays
- Participant files
- Pharmacy records
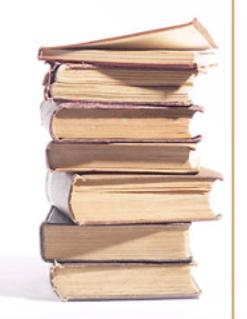
Incomplete data & record keeping:

- Missing or incomplete data
  - ? Data integrity
  - IRB may *inform* the PI that "data" may not be used
  - ? Participant at risk of harm
  - What is supporting findings

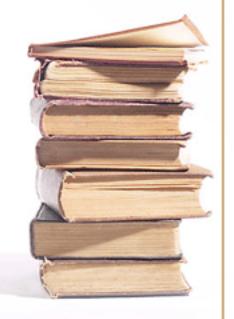# *Creating & Documenting on "Case Report Forms (CRFs)"*

- CRFs:

    - Used to collect & record study data

    - CRFs = SD: unless specified in study protocol

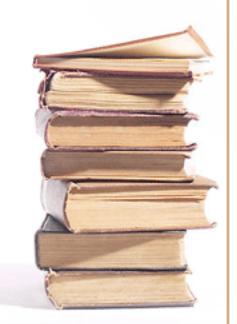   - Need a supporting SD to assure data is valid

Creation of CRFs

- PI:
  - Review CRFs
  - Sign & date
  - This works if there is a scheduled time to meet with PI.....weekly.....monthly....
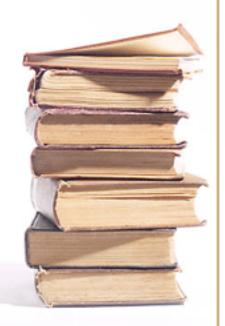
CRFs

- Do not:

  – Copy CRFs

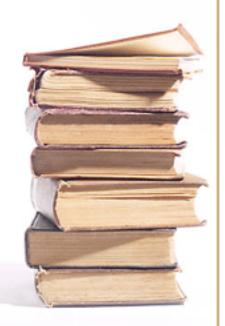 – Use them as flow sheets

  – Cannot cite them as a source

CRFs

- May want to create & pilot forms prior to implementation of study
- Record data on CRFs from source documents
  - Record data in real-time
- Can only collect data that has been approved by HRPO

Source Document Templates

- http://research.wustl.edu/Pages/default.aspx
    - Compliance areas
    - HSR QA/QI
    - Clinical Research Forms
        - View forms

Participant Research Record

- All communication
  - Log
    - Method
      - Phone call
      - Email – need approval

- Schedule:
  - Research procedures
    - Visits
    - Follow up calls

- Lab, pathology, x-ray, other reports
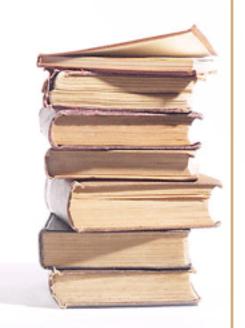
- Record of study med dispensed or device

Participant Research Record

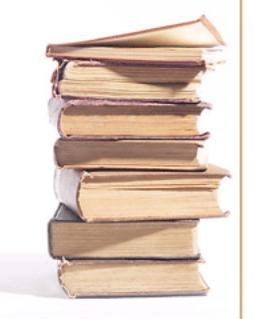- Copies of report sent to HRPO, if applicable

  - AEs/SAEs
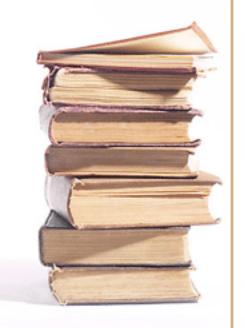
  - Protocol exemptions

  - Protocol exceptions

Test Article

- Definition:
  - 21 CFR 56.102 (l)
  - Any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the Public Health Service Act
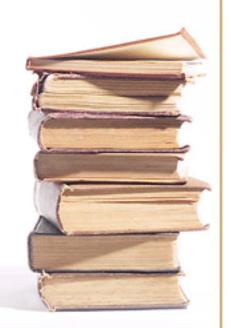
Study is Using a Test Article?

- Accountability
  - 21 CFR 312.62 (a)
    - A PI is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by participants
    - Account for:
      - Used products
      - Unused products
      - Returned products
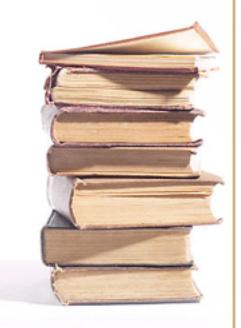   - Disposal – per protocol or sponsor

Accountability of Study Med

- Where is the drug coming from?
  - Shipping & receiving invoices
    - Type
    - Quantity
    - Date of shipment

- Will the pharmacy be involved?
  - Are they accounting for the drug?
  - Who is dispensing the drug?
  - Who is administering the drug?

- Defined in protocol?

Required Storage of Study Med/Device

- Med Storage:
  - Temp logs
    - Room Air
    - Refrigerator

- Device:
  - Who is responsible
  - Receipt
  - Count
  - Sign out
  - Tracking

Staff Responsibility

- Document on log:
  - Type
  - Quantity
  - Date of shipment
  - Expiration dates
- Dispensing log:
  - Study personnel dispensed
    - Name on Delegation of Authority Log
  - Quantity to participant
  - Waste
  - Return
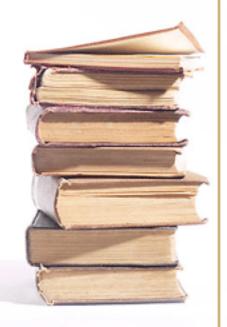 - Batch number/lot number
  - If any product wasted –done per policy

Participant Research Record

- Narrative note in participant research record:

  - Study med was dispensed to participant after participant signed the IC.

  - Dispensed per protocol.

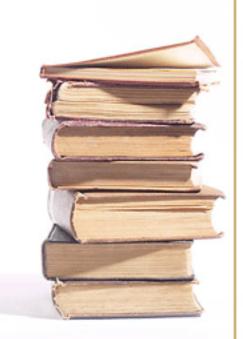 - Study med information given to participant

Mental Notes

- Keep test articles in locked storage
  - Access only by authorized study personnel
- Know the count and amount
- Document immediately:
  - Dispensing
  - Shipping, if applicable
- Inventory shipments upon arrival
- Check expiration dates….note!!!!
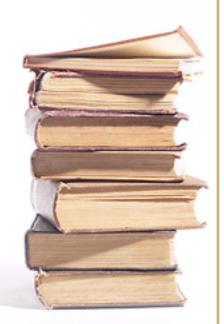- Document:
  - Dispensed
  - Unused
  - Waste

You Are Organized – You Are Collecting Data:

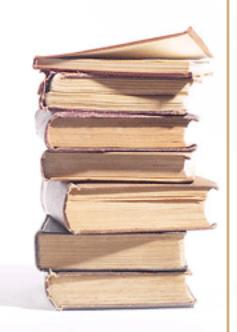## *Oops you made a mistake documenting.....*

- The "do not's"

  - White out

  - Multiple lines scratched through

  - Sign or date for anyone else

The "Write" Way to Make Correction

- 1 line through incorrectly written data

- Write corrected data point:
  - Next to incorrect
  - On top of

- Once Corrected:
  - Initial, date correction

- Make sure incorrect & corrected value can be seen

Study Files

- Document in "real time"

- Review documents for accuracy…..make it a practice

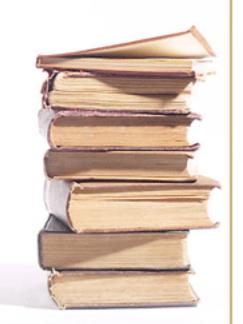- Review documents regularly during the trial
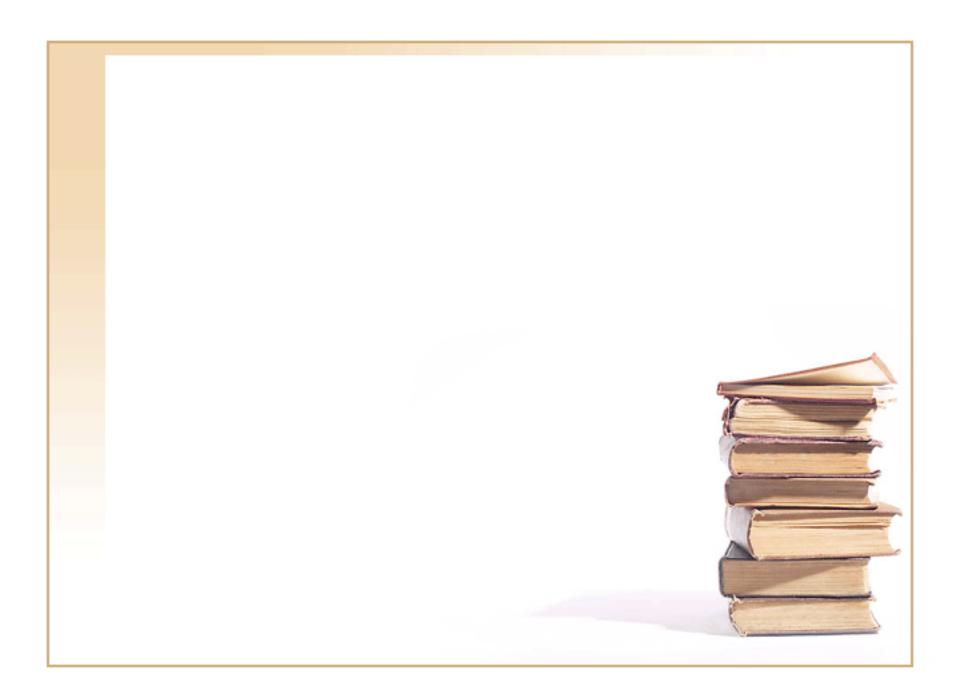
In Real Time

- Periodically review staff documentation

- Identify, address & resolve document issues asap

- End of study:
  - Inventory & archive documents
    - How long
  - Complete & submit appropriate study closure documents to HRPO (electronic)

In Closing

- Know your studies
  - Read & re-read

- Manage your files

- Routinely review data & SD

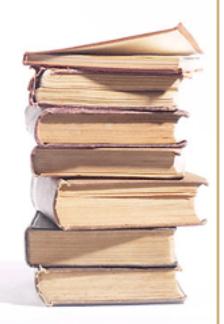- Keep on top of the tasks

- Ask for help

Review/Audits – Internal/External

- Most important step:
  - Do things correctly from the start
  - Organized files
- Informed of review/audit:
  - Amass study docs
  - Review study docs prior to review by review/audit team
    - IC
    - Participant research records (sampling)
    - CRF
    - Regulatory file
    - Other

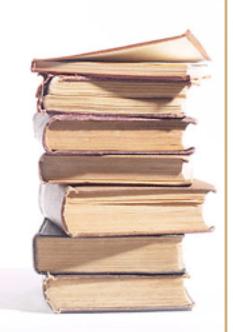- Only provide requested information requested by reviewers

Review/Audit

- Conduct of study:

  – Who did what

  – Degree of delegation of authority

  – Where specific aspects of study were performed

  – How & where data were recorded

  – How test article accountability was maintained, if applicable

Review/Audit

- Will review:
  - Diagnosis

  - Whether participants were properly diagnosed

  - Participant met inclusion criteria and no exclusion

  - Concomitant meds – allowed: not allowed

  - Follow up of AEs, if applicable

Review/Audit

- Reviewers will document findings

- Review findings

- Make corrections
  - May come back for re-review

Tell Your Research Story

Questions
?????

References

GCPs:

21 CFR 50, 54, 56, 312, 214, 812, 814

Common Rule:

45 CFR 46

Regulations:

- 45 CFR 46
- 21 CFR – FDA

NIH Guidelines

ICH GCP

HRPO Policies

Institutional Policies