Good Clinical Practice (GCP) Training: Best Documentation Practices for Clinical Research

Presented by:

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Objectives

1) Describe the regulatory framework for Good Clinical Practice.
2) Describe the importance of source documentation and common documentation pitfalls.
3) Understand the difference between regulatory binders and subject files.
4) Identify common errors in informed consent documentation.
5) Describe the elements of thorough documentation of adverse event assessment .

What is "Good Clinical Practice? (GCP)

- Guiding principal of clinical research
- "Standard for design, conduct, performance, monitoring, auditing, recording analysis and reporting of clinical trials in a way that provides assurance that the data & reported results are **CREDIBLE & ACCURATE** & that the **RIGHTS, SAFETY, and WELL-BEING** of trial **SUBJECTS are PROTECTED**." (21 CFR 312.12)

In GCP….

Quality Data = Patient (Subject)

Safety & Well-Being

THEREFORE

Poor Data, Poor Documentation=

Undermines Patient Safety & Well-Being

GCP Principle: "Quality Systems"

- Scientifically valid and ethically sound experimental design
- Adequate protection of subjects rights, safety, and welfare
- Qualified personnel
- "Adequate" monitoring
- Current, complete, and accurate data

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Where do we see GCP Standards in our guidances/regulations ?

- Federal regulations (45 CFR, 21 CFR.312/812)
- International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines
- Federal guidelines
- Institutional Policies & Procedures
- Departmental Policies
- Study protocol

Federal Regulations-Quick Review

- 45 CFR-also known as the "Common Rule"'
  - Regulates publicly funded research of human research subjects
  - Approved into law in **1981**
  - Defines vulnerable subjects
  - Overseen by DHHS (OHRP)
  - **Obama Administration released an update in January 2017. Compliance deadline delayed until July 2018.**

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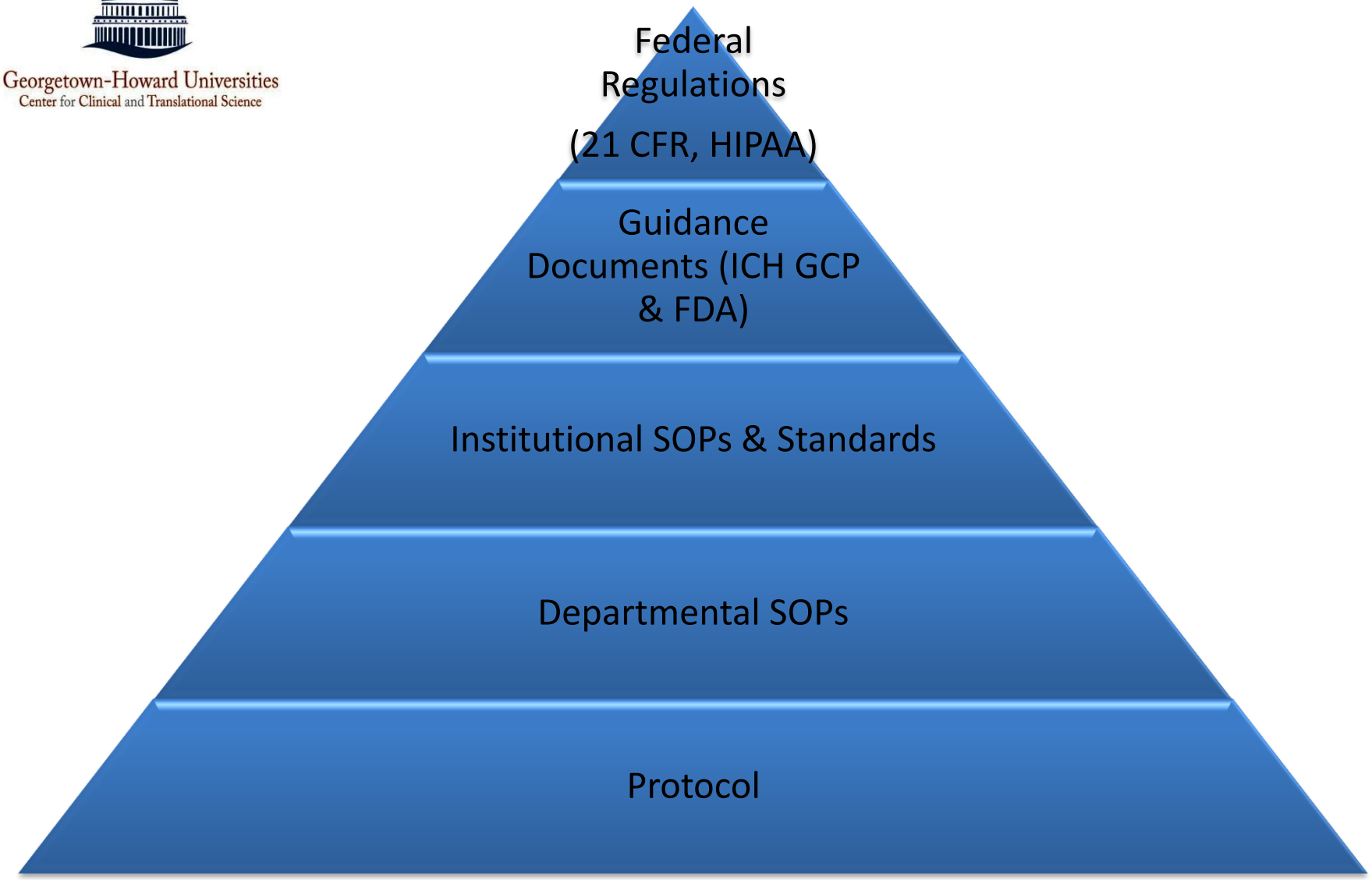
ICH GCP E6(R1)-1996

- Close-up view of research standards;
- Form the basis of research best practices
- Highly readable
- Section 8-”Essential Documents”
- Updated R2 version in June 2017
  - Certified copies; quality systems; risk-based monitoring


Federal Regulations (21 CFR, HIPAA)
Guidance Documents (ICH GCP & FDA)
Institutional SOPs & Standards
Departmental SOPs
Protocol

GU · HU · MHRI · ORNL · WDCVAMC

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Regulatory Binders

Regulatory Binders

- Contain the documents that demonstrate a team's compliance with applicable regulations & GCP.
- "Clean" binder says a lot to an auditor!
- OK if certain sections are located in a master file-but there should be a NTF stating this.
- Usually provided by sponsor, but is the Investigator's responsibility to maintain.
- If involved with an Investigator-initiated study, research team will need to create own binder.

Reg Binders-What goes in them?

- EVERYTHING & ALL VERSIONS OF EVERYTHING
  - Protocol
  - 1572/Statement of Investigator Compliance
  - Approved ICF Documents & all IRB approved materials (DON'T FORGET SUBJECT MATERIALS)
  - Investigational Drug Brochure
  - IRB Correspondence
  - Sponsor Correspondence
  - Monitoring Reports/DSMB Meeting Reports

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Reg Binder-Continued

- Research Team Qualifications/Training
  - CVs showing current job title!!
  - GCP Training (CITI)
  - Documentation of protocol-specific training:
    - New versions of protocol
    - Protocol-specific tests
    - Surgical/device training used in protocol

Study Drug/Device Documentation

- Usually maintained in a separate binder where investigational drug/device is stored;
- Will need 2 documents:
  - Documentation of temperature log for drug
    - Even if stored in room temperature!
    - What is your off-hours storage plan?
  - Accountability Documentation

Drug/Device Accountability

- Need to have documentation of receipt of drug/device from manufacturer in an inventory log;
- Accountability Log-tracks the dispensement of study drug to subjects.
  - Will track subject ID numbers, Lot ID numbers, Date dispensed & returned

Don’t forget the Delegation of Authority Log (DOA)!

- Delegation Logs are how PIs document delegation of trial responsibilities to QUALIFIED members of the research team who perform RESEARCH duties.
- Qualification is key.
- Tracks involvement dates of study team members.
  - PRO-TIP: Study staff should not be documented as performing study functions until AFTER date of protocol training.
- Don’t forget to update as research members leave!

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When are SOPs needed?

- Usually need to be written for investigator-initiated studies;
- Clearly formalize and provide guidance for research processes. Like an instruction manual.
- Normally see SOPs for:
  - Investigational Drug Management
  - Data Management
  - Informed Consent Process

A Note on "Note To Files"

- "Note to Files" (NTF) are used to "explain" problems in a research study that can't be corrected directly in the research documentation.
  - Should be used to describe problematic/deficient research operations/processes
  - Help "tell a story" to an auditor.
- HOWEVER: Don't misuse NTFs!
  - An abundance of their use is a huge red flag!
  - Should always document corrective action as well

Investigator Initiated Studies

- Will need to create documentation templates & formalize study processes into SOPs
- Requires more experience/training on the part of the research personnel to maintain compliance
- Documentation of end-user testing (validation) of electronic systems

Subject Files/Binders

- All subject-specific documentation is stored separately from regulatory binder. Usually in a file or a 3 ring binder.
- Will contain:
  - Original signed Informed Consent Forms & HIPAA Authorizations;
  - Screening forms; Inclusion/Exclusion forms;
  - Source Documentation (EMR Print-outs, Clinician Notes, Labs, Radiology Reports, etc)
- Study visit data
- Case Report Forms (CRFs)
- Notes to File regarding subject specific issues

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Subject File Organization

- Signed, original ICF & HIPAA Authorizations in front;
- Tabs:
  - Inclusion/Exclusion Worksheet & all supporting eligibility documentation;
  - Study Visits (recent first)-
    - For each visit, file any labs, radiology reports, ECGs, etc performed at that visit
    - Study drug administration/accountability
      - (FOR OUTPATIENT STUDIES: ARE YOU TRACKING COMPLIANCE?!)
    - Relevant Note to Files for that visit
  - Adverse Event Log & SAEs
    - File by each SAE

Subject Files-Certified Copies

- Certified Copy-copy of original information that has been verified as the “exact copy” by a dated signature or via a validation process.
  - Example: EMR Print-Out
    Method #1: EMR print-out displays the date/time & by the authorized user who printed out the copy. SOP/NTF would describe this as the certification process.
  - EMR printed out, with a memo stapled on top that states the print-out is an exact & valid copy of the original, and then signed/dated by the user.

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Informed Consent Documentation

Informed Consent Documentation

- Every informed consent document should have a corresponding note/checklist that documents the informed consent PROCESS
  - "Who, what, wheres"
  - More specifics in this note, the better;
    - Who was present for the consent process;
    - Which questions were asked
  - Documentation requirement: Subject given a copy of the ICF

Informed Consent Process Checklist

Check all that apply	
☐	The subject meets all eligibility requirements.
☐	Was the subject's comprehension assessed to ensure that the subject understands the research and the risks and benefits involved in the study?
☐	Subject was given a copy of the California Experimental Subjects' Bill of Rights.
☐	Subject signed the UC HIPAA Research Authorization for Release of Personal Health Information for Research.
☐	Discussed, explained and reviewed the consent form with subject. ❑ Written consent was obtained (per IRB approved consent process) ❑ Surrogate consent was obtained (per IRB approved consent process)
☐	All of the subject's questions were answered/concerns addressed. (document multiple subject contacts below) ❑ Subject did not have any questions/concerns
☐	Subject was given time to review the consent form and to discuss participation in this study with family members/others.
☐	The subject has agreed to participate in the study and signed/dated the most current valid IRB approved consent form *prior to the start of any study procedures*.
☐	A copy of the signed and dated consent form was given to the subject.
☐	The original signed and dated consent form was placed in the research record or separate binder.
☐	Was there early withdrawal from research participation? If yes, note reason.

Informed Consent (Continued)

- Attachment C
- Sample Language for Documenting Informed Consent Process
-
- NOTE: This example is a template in an electronic medical record.
-
- Name: John Smith
- Short Title: DP1822 CHAC
-
- The above named patient has volunteered to participate in the above named research study. This patient was counseled about their part in the participation of the research study and I have reviewed and discussed the informed consent form provided. This patient was given reasonable time to consider their decision to become a research participant in the absence of coercion or undue influence. The patient was given an opportunity to have their questions about the clinical trial and/or involved medical procedures answered. The Principal Investigator was available during the informed consent process to discuss the trial's risks, benefits and other aspects with the potential participant.
-
- In accordance with HIPAA, a Medical Records Release and General Authorization to Use and Disclose Health Information for Research was reviewed with, granted and signed by the patient.
-
- In accordance with FDA informed consent Regulations (21 CFR 50.27), the patient has been provided with a copy of the Informed Consent Form, which they have signed today, after reading it or having it read to them. A copy will also be filed in the patient's chart.
-
- No study related procedures were performed prior to the patient signing informed consent.
-
- Name and Signature of Person Obtaining Consent: Mary Jones
- Date: August 18, 2014
- Obtaining Consent: Mary Jones
- Date: August 18, 2014

Common Pitfalls
ICF Documentation

- Consent & HIPAA forms signature deficiencies
  - Missing signatures on last page
  - Not initialing the bottom of every page
  - Not checking box about participation in other research studies
  - No witness signature although required by IRB
  - Using member of research team as a witness
  - For inpatient studies, not reconsenting the subject if an LAR consented on behalf of the subject
  - **SOLUTION: At enrollment, have a 2nd party review the documents, along with inclusion/exclusion criteria.**

A “word” on verbal consent

- Still need a note in the subject file describing the informed consent process!

Electronic Consent

- Same content requirement as paper-based ICF;
- FDA regs require person signing the ICF should receive a copy, can be paper or electronic.
  - *The copy (e.g., printed paper document or email with an e-copy) should include a transcript of any audiovisual presentations provided during the eIC process. Should an e-copy be offered, subjects should be informed of the risks of storing or viewing the consent document on a personal electronic device (PED), especially if that PED is shared with other users or is lost, hacked or subject to a search warrant or subpoena.*

TIP

-

Common Pitfalls
ICF Process

- Using wrong version of ICF

SOLUTION: Don’t make pre-printed copies of ICF. Print only when ready to consent.

Common Informed Consent Pitfalls (continued)

- Not reconsenting a subject with a new version of a consent form when IRB requires.

SOLUTION:

1) Read IRB approval letters for new ICF versions very carefully;
2) Know why an ICF has been amended.

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Source Documentation

Source Documentation vs Case Report Forms

- What is Source Documentation?
  - Where you “show your work”, original form of data
  - FDA refers to source as “case histories”
- What are Case Report Forms (CRFs)?
  - Final place where data is recorded
  - May be on paper or electronic
- There should always be a source for CRFs!
  - When exception: A note to file should be written

Source Documentation

ALCOA-C-Defined in ICH GCP E(2)

- **A**ttributable (Who created the record?)
  - MAKE SURE SOURCE DOCUMENTATION IS SIGNED BY THE PERSON WHO GATHERED THE DATA!!
- **L**egible
- **C**ontemporaneous: DON'T BACKDATE!
- **O**riginal
  - Source is where data is first recorded. Could even be a sticky note!
- **A**ccurate: Make sure source data don't conflict

- **C**omplete: Complete all of the data fields, or write "ND" –Don't leave anything blank!

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More on Source Documentation

- Need to build a story with your source data
  - "If it wasn't documented, it wasn't done."
- Good source data is key to protocol compliance.
  - Look at protocol schedule of events for hidden "easter eggs."
- Checklists are your friend!

Laboratory Results Review

- For any protocol-required labs, an Investigator should sign off indicating his/her review.
- Additionally, any abnormal values should be labeled as “CS” (Clinically Significant) or NCS “Not Clinically Significant.”
- Any labs labeled “CS” would then become adverse events.

How should you correct a mistake in clinical research?

In source documentation, you wrote a study visit as 4/7/14. After review, you confirm that the visit actually occurred on 5/7/14 and you now need to correct your CRF. How would you do this?

- Scribble out the date you wrote and then write the correct one next to it.
- Try to change the date that you wrote by writing over the numbers to indicate 5/7/14.
- Draw a line through the previously written date, initial and date next to it, then write the correct date of 5/7/14.
- Use correction tape to go over the previous date and then write the correct date over it.

Inclusion/Exclusion Documentation

- A checklist of inclusion/exclusion criteria should be used. Signed off by CRC & PI.
- Each criterion should have supporting documentation, whether it be in EMR or a PI note.
  - Be careful of criteria that is somewhat nebulous!

Inclusion/Exclusion Documentation

III. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation***
1.	☐	☐	
2.	☐	☐	
3.	☐	☐	
Exclusion Criteria (From IRB-approved protocol)			
II.	☐	☐	
III.	☐	☐	
IV.	☐	☐	
V.	☐	☐	

IV. Statement of Eligibility

This subject is ☐ **eligible** / ☐ **ineligible** for participation in the study.

Signature:	Date:
Printed Name:	

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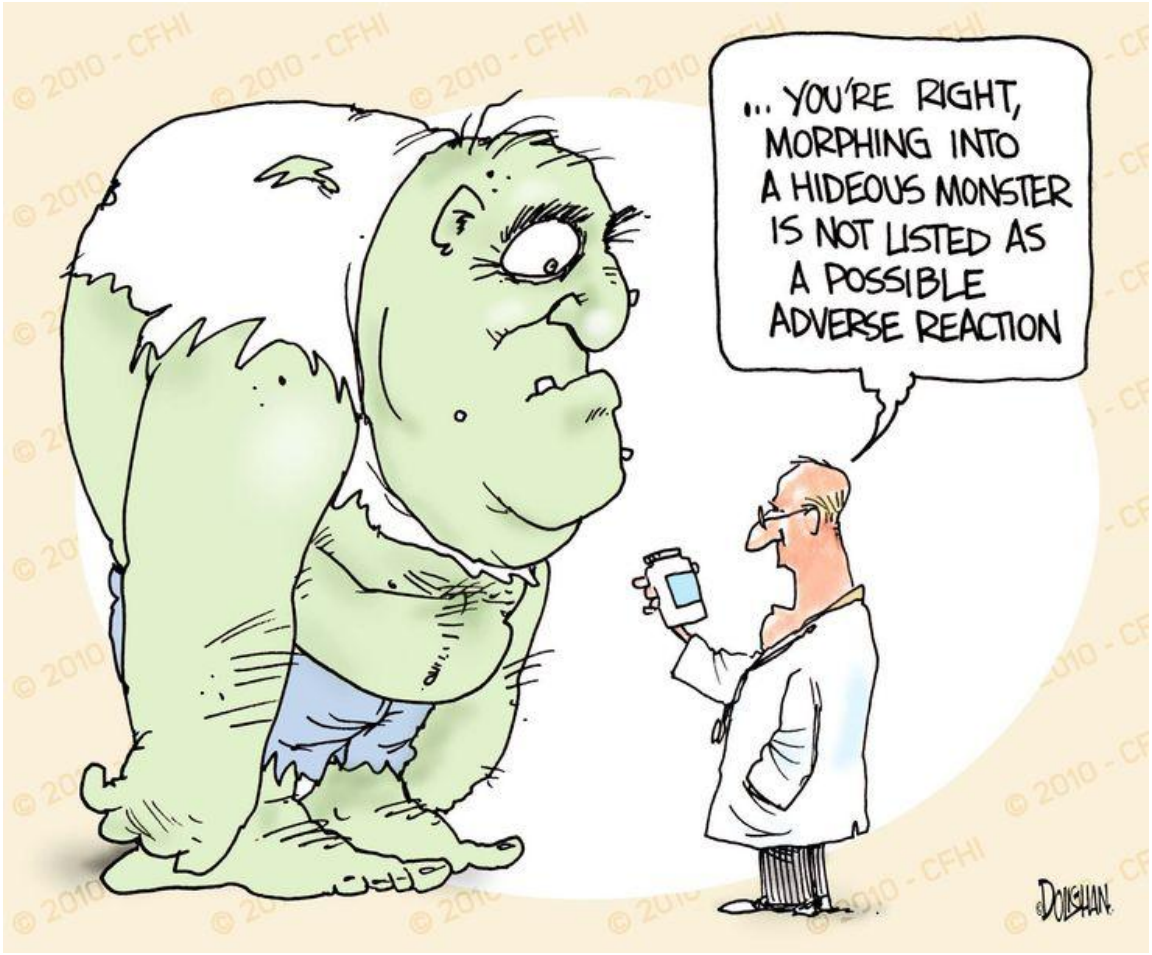
Adverse Events



Adverse Event: Definition

- Adverse event: “Any untoward event that occurs after enrollment”
- MAY NOT BE AT ALL RELATED TO STUDY INTERVENTION, may even be a common clinical occurrence;
- BUT it must be documented to indicate PI is aware & has evaluated event.

Tracking Adverse Events

- An AE is any change in baseline
- First step in tracking this change:
  - A thorough list of baseline conditions!
    - Example: asthma
      - Mild asthma exacerbations doesn't need to be documented; but hospitalization for asthma does need to be recorded
      - HINT: Look at concomitant meds!

How to document AE evaluation?

- Utilize an AE Assessment Report in REAL TIME, also important to have back-up source. This is a tool—not the entire record.
- Investigator should be completing evaluation fields!

Adverse event	Start and stop dates	Serious	Severity (Oncology Studies, Use CTCAE 1-5 system)	Relationship to study agent	Anticipated	Action taken with the study agent	If Serious, date PI became aware	Was the SAE reported to the sponsor?	Was the SAE reported to the IRB?	PI initials and date	Comments /PI Initials at AE Closure
	Start: Stop:	☐Yes ☐ No		☐Not related ☐Possibly related Related ☐Related ☐Unknown	☐Yes ☐ No	☐ None ☐ Reduced ☐ Interrupted ☐ Discontinued ☐ Other:		☐ No ☐Yes Date:	☐ No ☐Yes Date:		

Serious Adverse Events (SAEs)

Definition of **Serious** Adverse Event:

- AE that results in one or more of the following outcomes:
  - Death;
  - Life threatening condition;
  - Permanent Disability;
  - Inpatient Hospitalization (24 hours or more)
  - Congenital Anomaly/Birth Defect

"Relatedness" of AE

- "Not related, possibly related, related or unknown"
- The Investigator should look at the AE in relation to:
  - **Timing** of AE with study agent;
    - » Did the AE onset begin at same time or in close timing with study intervention?
    - » Did the AE dissipate or improve after the study intervention was stopped?
  - **Underlying medical condition**(s) of research participant;
    - » Example: Pitting edema related to history of CHF, not study drug.
- BEST PRACTICE: Documentation of Investigator's evaluation of why AE is not related to study

Common Pitfalls
Adverse Event Reporting

- AEs not properly reported to IRB or sponsor.

SOLUTION:

Intimately know the study protocol!

Read your IRB's adverse event reporting policy!

Determination of AE's "Expectedness"

- Expected or unexpected;
- If EXPECTED:
  - Should see the AE listed as a known side effect in the protocol, ICF, or package insert;
- If UNEXPECTED:
  - Not a known risk of the study agent, won't be listed in study documents

Difference between Recording & Reporting AEs

- All AEs should be recorded,
- But not all AEs are reported to IRB!
  - Know your IRB's reporting requirements!

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When do AEs need to be reported promptly to the IRB? (within 7 days of PI becoming aware)

EXPEDITED REPORTING:

- When AEs are:
  - Serious
  - Related or possibly related to study;
  - AND Unexpected

- Should document in study record when PI became aware of SAE

AE Documentation: Pro Tips

- An AE that worsens into an SAE is a separate event—i.e. the SAE will have a start date that is the stop date of the AE.
- PIs need to be aware of what they're signing off on the AE Log!! If the AE is thrombocytopenia, then the PI should be identifying the low platelet count on the lab sheet as "Clinically Significant."

AE Documentation Pro Tips

- Ideally, AEs should be spontaneously reported or elicited from subject.
  - Use open-ended questions, don't ask about specific symptoms
- Look at lab values from week to week. If trending in a specific direction, is this being addressed by PI? Weight, too!
- Have subjects sign an IRB approved medical release form at enrollment

Internal Audits: Acceptable-Y or N?

- Only one physician listed on 1572 for study-i.e., no co-investigators.
- Subject consented with wrong version of ICF. Subject re-consented with new version. Study team throws away previous version of signed ICF.
- Protocol includes digital photography of wound with study camera during follow-up visit. Instead, PI uses cell phone to take pictures.
- Subjected re-consented with new ICF form. New HIPAA authorization form not signed.
- Protocol requires physical exam on Day 7, but not Day 14. Physical exam performed on Day 14 by Co-Investigator.
- PI assesses abnormal lab value as “CS” and does not add abnormality to AE Log.

Acceptable-Y/N?

- Study drug stored at room temperature in locked cabinet. Thermometer breaks and not monitored for three days. Study drug dispensed during this time.
- PI assesses an AE as serious, related and expected. Research team does not report SAE to IRB.
- IRB approval lapses, but CRC conducts telephone follow-up visit.

Resources

- 1996 ICH GCP Guidelines, especially Section 8
- MHRI Policies & Procedures (found on Starport)
  - Adverse Event Reporting Policy
  - Source Documentation Procedure
- FDA responses to GCP questions (Easiest way to find website is to google).

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Questions?

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