

Gotcha!

What Gets You in Trouble in GCP Audits and How to Prevent the Pain

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18 May 2007

Agenda

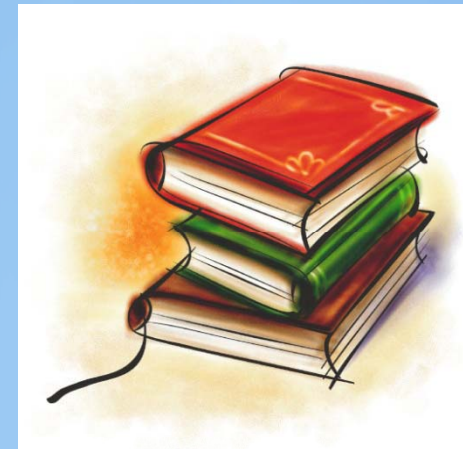
- **Setting the Scene**
- **Tiers of Trouble**
- **Chilling Consequences**
- **Exemplary Examples**
- **Preventing the Pain**

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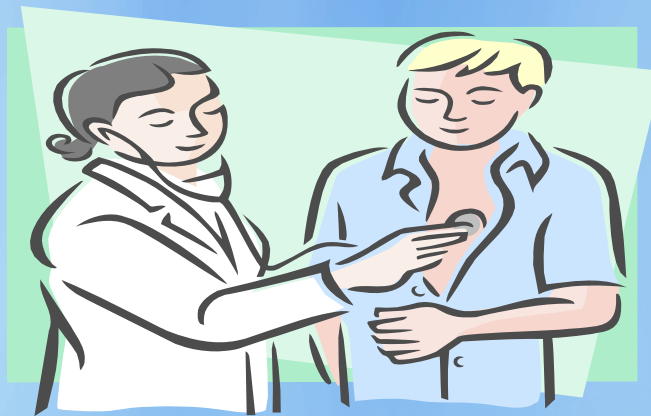
Rules, Rules, Rules

- Food & Drug Administration (FDA)
- European Medicines Agency (EMA)
- Department of Health and Human Services (HHS)
- Office for Human Research Protection (OHRP)
- National Institutes of Health (NIH)
- Institutional Review Board (IRB)
- Contract Research Organization (CRO)
- Corporate sponsor
- Health agencies from other countries
- Source of funding



Research Subjects

- A human who participates in an investigation, either as a recipient of the investigational drug/device or as a control
- A subject may be a healthy human or a patient with a disease
- Human subjects are alive (vs. decedents)
 - Includes medical chart reviews, tissue collection



Clinical Practice vs. Research

Patient

- Suffers from a disease
- Goal is treatment of patient
- For personal benefit
- Standard care

Subject

- Participant in research. May healthy or not.
- Goal is characterization of medication/device
- For societal benefit
- Not standard care

Clinical Practice vs. Research

Patient

- Standard care
- Approved treatment
- Treatment changes permitted
- Can make life changes at will
- Records reflect care

Subject

- Not standard care
- Unapproved treatment or placebo
- Treatment changes not permitted
- Must stay as stable as possible
- Record keeping extensive and audited

Publication vs. Submission

ALCOA

Pub

Info

IRB

Ethi

PMA

e

Expectations: Objective Evidence

- ALCOA principle of data quality:
 - **A**tributable
 - **L**egible
 - **C**ontemporaneous
 - **O**riginal
 - **A**ccurate
- If it's not documented then it didn't happen and it doesn't exist
 - Anecdotal reporting – don't even try!
 - Informal documents (not controlled and signed) not acceptable either; e.g. email
- Traceability: follow data each step of the way

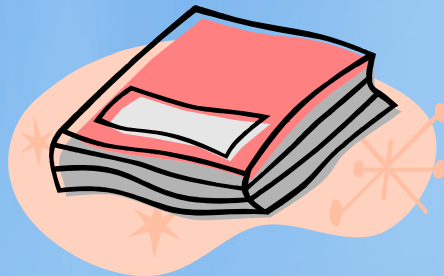
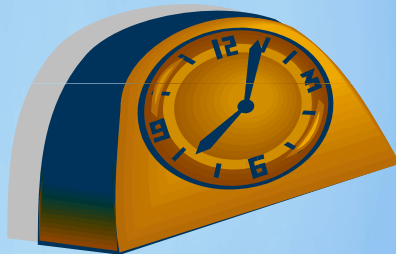


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Noncompliance Usually Not Intentional...

- Lack of resources (staff, time, subjects)
- Inexperienced study staff
- Lack of GCP training and/or regulatory oversight
- Faster and cheaper studies= no time to document properly
- Lack of PI oversight
- Academic advancement, pressure to publish
- Financial temptations



Definitions



- Deviations:
 - Changes in the study plan and procedures that are not consistent with the approved protocol
- Errors:
 - An act(s) involving an unintentional deviation from truth or accuracy
- Misconduct:
 - Intentional wrongdoing
- Fraud:
 - Intentional perversion of truth in order to induce another to part with something of value or to surrender a legal right

Stan Woollen's Misconduct Scale

- **Innocent Ignorance**- misconduct of the uninformed kind
 - Noncompliance based on *lack of understanding* the regulatory consequences of an action. The act itself is usually intentional but the noncompliance is unintentional, not usually done to deliberately deceive
 - Backdating the subject's signature on a consent form because the subject forgot to date the form originally and the monitor is coming tomorrow!



Stan Woollen's Misconduct Scale

- **Surprising Sloppiness-**
misconduct of the lazy kind
 - Noncompliance due to *inaction*, inattention to detail, inadequate staff, lack of supervision. The act itself may be intentional or unintentional, the noncompliance is unintentional and usually repeated
 - Blood pressures rounded to the nearest 5mm
 - Data inaccurately transcribed or recorded



Stan Woollen's Misconduct Scale

- **Malicious Malfeasance-** Misconduct of the sleazy kind
 - Usually noncompliance due to deliberate action to deceive or mislead
 - ***Falsification of data*** in proposing, designing, performing, recording, supervising or reviewing research, or in reporting research results.
 - Falsification of data includes creating, altering, recording, or omitting data in such a way that the data do not represent what actually occurred.



Sources of Issues

- **Acts of omission**
 - not revealing all data (e.g. reportable adverse events, concomitant meds., etc)
- **Acts of commission**
 - altering or fabricating data (e.g. lab values, BP readings, non-existent specimens)
- **“Data” is interpreted broadly**
 - individual facts, statistics, tissue samples, items of information, statements made by individuals

Note: Research “misconduct” does not include honest error or honest differences of opinion

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Establishment Inspection Reports (EIR)

- **NAI: No Action Indicated**
 - No significant deviations from the regulations found: No response required
- **VAI: Voluntary Action Indicated**
 - Findings of deviations from regs and GCP
 - May or may not require a response, letter will specify and identify contact person
- **OAI: Official Action Indicated**
 - Warning letter – “483”
 - Identifies serious deviations from the regulations
 - Requires prompt action
 - FDA may take regulatory and/or administrative sanctions

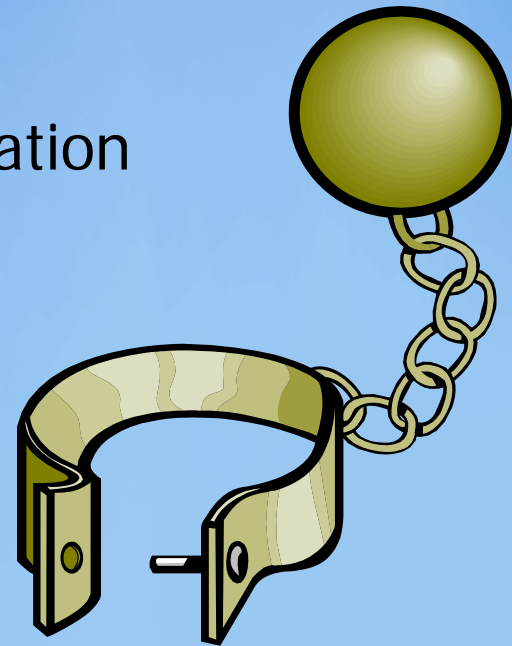
Minor violations

- Letter specifying issues, degree of seriousness and expected response
- Provided that robust plans are developed and implemented to remedy issues, process is usually closed out through correspondence
- Increased probability of repeat inspection



Major Findings

- Warning letter, FDA Form 483
- Re-inspection
- Termination of IND
- Refusal or withdrawal of approval
- Sponsor/CRO/Investigator disqualification
- Test article seizure
- Injunction
- Prosecution
- Jail



http://www.fda.gov/ora/compliance_ref/debar/

Name Address	Center	Type	Action Date	Comments
ROGER D. ANDERSON, MD PITTSBURGH, PA	CDER	D	10-JAN-2005	By consent agreement
EDUARDO CARO ACEVEDO, MD BAYAMON, PR	CDER	D	30-JUL-2002	Through hearing process
CARL ANDREW DeABATE, MD WASHINGTON, DC	CDER	D	05-FEB-2004	By consent agreement
HAROLD F. FARBER, MD NARBERTH, PA AND PHILADELPHIA, PA	CDER	D	18-JUL-2005	By consent agreement
ROBERT A FIDDES, MD WHITTIER, CA	CDER	D	01-JUN-1999	Through hearing process
JAMES A. HALIKAS MINNEAPOLIS, MN	CDER	D	15-JAN-2001	Through hearing process
LEON C. LaHAYE, MD LAFAYETTE, LA	CDRH	D	18-JUN-2002	Through hearing process

D: Disqualified or totally restricted clinical investigators who are not eligible to receive investigational products.
R: Restricted

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Audit Findings

- Deficiencies identified in FDA audits regarding the rights and welfare of the subjects include:
 - Failure to obtain subject consent
 - Inadequate subject consent (about 50% of all audits)
 - Failure to communicate with the IRB on changes and progress reports (approximately 11%)
 - Failure to report adverse events (approximately 7%)



Audit Findings

- Deficiencies identified in FDA audits regarding the rights and welfare of the subjects also include:
 - Inappropriate payment to subjects
 - Use of drug before IND submission
 - Failure to obtain IRB approval
 - Inappropriate delegation of investigator's authority
 - Failure to list additional investigators on the 1572



Audit Findings

- Deficiencies in the integrity and validity of data include:
 - Protocol deviations (approximately 40% of all audits)
 - Inadequate and inaccurate records (approximately 38%)
 - Inadequate drug accountability (approximately 25%)
 - Submission of false information (approximately 12% of “for cause” inspections)
 - Unapproved concomitant therapy (approximately 8%)
 - Simultaneous use of multiple investigational drugs
 - Problems with records availability

The Risks of Delegation

If you sign a FDA Form 1572 YOU MUST:

- Personally conduct or supervise the investigation
- Ensure that all persons assisting in study conduct are informed about their obligations
- Comply with all requirements regarding obligations of clinical investigators

**You may delegate authority,
but
you cannot
delegate responsibility**

Warning Letter Examples

1. FAILURE TO PROTECT THE RIGHTS, SAFETY, AND WELFARE OF SUBJECTS UNDER YOUR CARE [21 CFR 312.60].

Subjects enrolled in protocol [] were randomized to receive either aspirin (81 mg, 325 mg, or 650 mg) or placebo. Because aspirin is associated with gastrointestinal (GI) bleeding, which can be serious or even fatal, the protocol excluded subjects with known risk factors for GI bleeding. In particular, the protocol excluded “[s]ubjects who have a current, or within the past year, clinically significant medical history of gastrointestinal disease including gastritis, gastric ulcers, peptic ulcer disease, gastrointestinal bleeding, [or] inflammatory bowel disease” and

During the study, this subject presented to another physician with complaints of hematemesis (vomiting blood) and blood in her stool. The subject was diagnosed with a GI bleed of such severity that she was hospitalized from September 27 to October 1, 2001 and required transfusion of three units of blood

- The subject had a history of peptic ulcer disease and an episode of gastrointestinal bleeding in October of 2000, as documented in your medical progress note dated 10/23/00, and in the monitor’s letter dated 10/31/01.
- At the time of enrollment, the subject was taking Celebrex® a COX-2 inhibitor for a degenerative arthritic condition, as documented on the Screening/Baseline Source Document Worksheet dated 7/11/01 and in the monitor’s letters dated 8/23/01 and 8/26/01.
- The subject had a known allergy to Anacin®, an aspirin containing product, as documented in your medical progress note dated 4/10/01, in the monitor’s letter dated 10/31/01, and in a Memo to File dated 12/27/01.

2. FAILURE TO PERSONALLY CONDUCT OR ADEQUATELY SUPERVISE THE ABOVE-REFERENCED CLINICAL TRIAL [21 CFR 312.60].

There is also no indication that you ever personally conducted the study.

- b) You delegated certain study tasks to an individual not qualified to perform such tasks.

You permitted an individual with no medical training (Ms. [REDACTED]) to evaluate laboratory results for clinical significance. These lab reports were not co-signed by you; therefore, there is no indication that you reviewed them.

Your lack of supervision and personal involvement, and inappropriate delegation of study tasks, resulted in failure to protect the rights, safety, and welfare of study subjects, failure to adhere to the study protocol, failure to maintain adequate and accurate study records, and failure to promptly report serious adverse events to the sponsor and IRB.

subject's post-menopausal status) dated 7/24/01 and 8/4/01.

3. FAILURE TO CONDUCT THE STUDY IN ACCORDANCE WITH THE INVESTIGATIONAL PLAN [21 CFR 312.60].

- f) The protocol required that the clinical investigator review all available assessments including ECG results, vital sign measures, physical exam results, current medications and coexistent medical conditions at the screening/baseline visit to ensure that subjects satisfied the inclusion/exclusion criteria. Available records indicate that you ~~did not perform or review the required subject assessments in accordance with the protocol.~~ It appears that you reviewed some of these assessments after study completion. These tasks were performed by your study coordinator and sub-investigator.

4. FAILURE TO PREPARE AND MAINTAIN ADEQUATE AND ACCURATE RECORDS [21 CFR 312.62(b)].

You failed to ensure that source documents and case report forms (CRFs) generated during the conduct of the study were adequate and accurate as follows:

- a) For subject 233, who met ~~multiple exclusion criteria as noted under item 1~~, the Source Document Worksheet for the screening/baseline visit, dated 7/11/01, was marked that the subject met all inclusion/exclusion criteria. In addition, weights of 301 lbs. and 294 lbs. were reported in medical records dated 4/10/01 and 9/27/01, respectively. However, the subject's weight recorded in the source document worksheet and the CRF for the screening/baseline visit on 7/11/01 was 166 lbs.
- b) For subject 295, apart from the signed consent form and the screening/baseline worksheets, the case history did not contain any other documents to validate the subject's enrollment and completion of the clinical investigation. From the enrollment log, this subject completed the study on 11/1/01.

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Avoiding the Disbarred List!

- Have an independent auditor do a 'friendly' audit
- Review warning letters on FDA's website
- GET TRAINING in areas of common findings
- Read and discuss ICH E6
- Don't take monitor findings personally - use them as a tool for improvement
- Document, document, document
- Review FDA audit instruction manuals



FDA Audits: Source Document Verification

- All subjects signed informed consents prior to their participation in the study
- The subjects randomized into the study were diagnosed with the disease defined in the protocol
- The subjects met all study inclusion criteria and none of the study exclusion criteria
- Data in the CRFs are supported by source documents

FDA Audits: Source Document Verification

- All SAEs/AEs were adequately documented in the source documents and CRFs, and were reported to the sponsor and IRB in a timely manner
- All safety reports were promptly submitted to the IRB
- Sponsor permission is documented to grant or deny permission for a protocol waiver
- Protocol deviations are documented and have been submitted to the IRB
- All corrections are made with a line across the error and the correct data is written either above, below, or to the side. Corrections are all initialed and dated.

FDA Audits: Review of Investigator Obligations

- Did the investigator appropriately delegate study activities and responsibilities?
- Did the investigator appropriately supervise site personnel?
- Was the study conducted at the approved location?
- How and where were the data collected and recorded?

FDA Audits: Review of Investigator Obligations

- How and where was the study drug kept?
- Was the IRB appropriately informed of protocol amendments, study progress, and safety concerns?
- Were AEs/SAEs managed appropriately?
- Were concerns identified by the CRA responded to promptly and appropriately?

Summary: Mistakes Happen

- Identify the mistake
- Acknowledge the mistake
- Correct the mistake, if appropriate
- Report the mistake, if warranted
 - Inform study team
 - Note to file
 - Chart note
 - Sponsor notification (don't forget to document)
 - Protocol deviation (IRB notification), if appropriate

References

- www.fda.gov
- Northwestern Center for Clinical Research, CRC Basic Training Course, 2006
- Stan Woollen, "Misconduct in Research: Innocent Ignorance or Malicious Malfeasance." www.fda.gov/oc/gcp/slideshows/2003/gcp2003.ppt
- Stan Woolen & Antoine El Hage, "Scientific Misconduct: the F Word." 2001 www.fda.gov/oc/gcp/slideshows/misconduct2001/misconduct.ppt
- Code of Federal Regulations

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