Noncompliance and Research Misconduct

- An honest difference of opinion or an honest error can result in the occurrence of isolated GCP noncompliance. This is NOT research misconduct.
- Misconduct requires deliberate or repeated noncompliance with GCP requirements.
- Even here there is a gradation of concern...
The “Misconduct” Scale

- Innocent Ignorance
- Sloppiness
- Malicious Intent: Falsification/Fraud

Malicious Intent: Falsification/Fraud

- Worst case scenario
- Generally a deliberate action to deceive or mislead
- Broad implications
- Low incidence, but great risk to GCP and the research enterprise
- Hard to detect/Hard to manage
Ways That Data is Falsified

- Creating data that were never obtained
- Altering data that were obtained by substituting different data
- Recording or obtaining data from a specimen, sample, or test whose origin is not accurately described or in a way that does not accurately reflect the data
- Omitting data that were obtained and ordinarily would be recorded

Who Does It?

- Anyone at the investigator’s site who has access to data
  - Principal Investigator
  - Subinvestigators
  - Study Coordinators
  - Study Nurses
  - Monitors sent from the Sponsor
Types of Data Falsified

- ECGs
- Blood Pressure Data
- Physical and lab examinations
- Biological Specimens
- Subject Identities
- Drug Compliance Records
- Most any other data...

Omitting Data: Where Have the Source Documents Gone?

- “They were destroyed in a hurricane”
- “They were lost in a boating accident”
- “They were lost in the mail”
- “The mover threw them out”
- “They were stolen”
Why is Data Falsified?

- Reasons are not always known or clear
  - To qualify ineligible subjects to enroll or continue on the study ("good of the subject")
  - To please the sponsor by filling in the blanks and making the source documents match the Case Report Form
  - To save time or to make a profit

Consequences of Falsification -1-

- If falsification takes place during a clinical study, it places all subjects in that study at possible safety risk
- Falsification jeopardizes the reliability of submitted and/or published data and undermines the regulatory authority’s mission to protect and promote public health
  - False basis for product approval; inaccurate information in the product label
Consequences of Falsification -2-

- Falsification may also have a far-reaching negative impact on clinical research
  - Decreasing public confidence and willingness to participate as subjects
  - Tendency for “falsifiers” to work on multiple studies involving multiple investigational products and often multiple sponsors

<table>
<thead>
<tr>
<th>CI</th>
<th>Applications</th>
<th>Sponsors</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>91</td>
<td>47</td>
</tr>
<tr>
<td>B</td>
<td>49</td>
<td>25</td>
</tr>
<tr>
<td>C</td>
<td>43</td>
<td>21</td>
</tr>
<tr>
<td>D</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>E</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>F</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>
Dealing with Falsification

- Prevention
  - Identify and eliminate/minimize risk factors for falsification
- Detection
  - Monitor and recognize signs of falsification
- Correction
  - Promptly investigate and report falsification

A CASE STUDY:
Lessons for Detecting Falsification
Outcome of the Case

- Guilty: Making false statements in a matter within the jurisdiction of the FDA
- Guilty: Conspiracy to commit an offense against the United States
- Penalties
  - Clinical Investigator sentenced to 15 months in prison
  - Fined US$ 800,000

Background to the Case

- CI conducted over 200 studies for as many as 47 drug companies beginning in the early 1990’s
- Bought bacteria from a commercial supplier to create qualifying cultures
- Diluted urine from staff member with benign proteinuria to qualify other subjects
- Pulled pages from patients’ medical charts making reference to disqualifying conditions
Media Attention

- National (U.S.) and international press coverage
- New York Times Article
  - “Research for Hire: A Doctor’s Drug Studies Turn Into Fraud”

From the New York Times -1-

- Letter from one of the testing company’s study monitors:
  - “CONGRATULATIONS on meeting your enrollment deadline!” the monitor wrote in a letter. “I performed a 100 percent source document verification (x-rays) and found no outstanding issues.”
Lessons Learned -1-

- To detect falsification, it is necessary to get technical
  - Read and evaluate x-rays, ECGs, laboratory results
  - Don’t just inventory the source documents

From the New York Times -2-

- “When a monitor hired by (XXX) asked to see the patient’s medical chart, a study staff member quickly fetched the patient’s medical chart, and pulled out every page that made reference to the disqualifying lung disease. Then, according to investigative documents, she turned the remaining records over to the monitor. The violation went undetected.”
Lessons Learned  -2-

- Question missing dates, times, information
- Question missing or out-of-sequence records
- Offer to retrieve records yourself

From the New York Times  -3-

“Even when his employees spelled out their suspicions (to monitors) about what was happening, it wasn’t that he was particularly adept at dodging their questions. Rather, they seemed reluctant to challenge such a prominent figure in the drug-testing business.”
Lessons Learned  -3-

- Don’t be intimidated
- You may need to challenge or confront the investigator
  - See if and what he/she tries to cover up when challenged

From the New York Times -4a-

- “Several former coordinators for [Dr. F] said they had reported his unethical conduct to an independent study monitor working with (XXX). The study monitor sharply challenged [Dr. F] and his staff in her reviews of their paperwork. [Dr. F] chafed at the challenges, feigning outrage.”
From the New York Times -4b-

“‘Our integrity and reputation for performing high-quality clinical trial work has been injured, and we are justifiably upset,’ [Dr. F] wrote in a letter to the sponsor, complaining about the monitor’s demand. He insisted the sponsor ‘have a new monitor assigned to our site immediately.’”

Lessons Learned -4-

- Believe the monitor and others who may come forward with complaints or suspicions
- Put the burden of proof on the clinical investigator
From the New York Times -5-

- “[Dr. F] replied that they were going to blame the study nurse for all of the problems, and he was going to say he had no knowledge of what was going on.”

Lessons Learned –5a-
Blame is Often Shifted

<table>
<thead>
<tr>
<th>Party</th>
<th>Blame Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Coordinator</td>
<td>39%</td>
</tr>
<tr>
<td>Study Nurse</td>
<td>17%</td>
</tr>
<tr>
<td>Hospital</td>
<td>4%</td>
</tr>
<tr>
<td>Sponsor</td>
<td>4%</td>
</tr>
<tr>
<td>Self</td>
<td>9%</td>
</tr>
<tr>
<td>Office Staff</td>
<td>9%</td>
</tr>
<tr>
<td>n (parties blamed) = 23</td>
<td></td>
</tr>
<tr>
<td>n (cases) = 20</td>
<td></td>
</tr>
</tbody>
</table>

17%
Lessons Learned -5b-

- Be suspicious of blame shifting
- Tell the clinical investigator that he/she is responsible for the conduct of the study and is accountable for the results

From the New York Times -6-

- “Why was [Dr. F] able to fool the monitors so easily? Because the oversight system is mostly designed to catch errors, not fraud.”
Lessons Learned  -6-

- Expect fraud
- Start from the assumption that the records are bogus and the study is fraudulent, and work back
- Let the records and your inspection restore your confidence that the work is NOT fraudulent

From the New York Times -7-

- “The FDA investigators asked [Dr. F] ...what could the watchdogs have seen that would have allowed them to detect his fraud.”
- “‘Nothing’, [Dr. F] replied. Had it not been for a disgruntled former employee, he would have still been in business.”
Lessons Learned -7-

- Cultivate “whistleblowers”
- Establish rapport with the study staff
- Be approachable and available; listen to grievances; observe working conditions

From the New York Times -8-

- “Avoiding Detection: The FDA Ignores an Early Warning”
- “The government had its first solid lead on what was happening in [Dr. F’s] office fully 17 months before Ms. X exposed his crimes to an FDA auditor.”
Lessons Learned -8-

- Have a system (with procedures) in place to capture, document and deal with complaints of misconduct in a timely fashion
- All complaints should be assumed to be credible unless demonstrated to the contrary after thorough evaluation and supervisory review
- The receipt, follow-up, and action on all complaints should be documented so that all decisions and actions can be reconstructed

Falsification/ Fraud: More Case Examples
Falsified Subjects

- Same subject enrolled more than once under two different names and identities
- Nonexistent subjects created
- Subjects fabricated from names in the obituary column of the local newspaper

Falsified Specimens

- Genetic analysis of sputum samples from 26 subjects showed only 3 distinct profiles
**Falsified ECG’s**

- Continuous ECG strip run on one patient then torn in half and represented as coming from two subjects
- Preprinted subject identifying information altered or obliterated
- Multiple subjects with identical ECG’s (“Dr. Xerox” will see you now...)

**Falsified Outcome Data**

- “The case report for patient #20 indicates he died in June 1985. The hospital medical records for this patient as of April 1996 indicate he swims and goes to the gym twice a week.”
### Perfect Results: Healing Esophageal Erosions

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Baseline Endoscopy</th>
<th>Healed Week 4</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
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<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

### Even Worse?

- Clinic has no endoscope/endoscopy suite to perform the procedures
## Vital Sign Determinations

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Study Day</th>
<th>Heart Rate</th>
<th>Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>100</td>
<td>110/70</td>
</tr>
<tr>
<td>9</td>
<td>100</td>
<td>110/70</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>100</td>
<td>110/70</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>100</td>
<td>110/70</td>
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</tr>
<tr>
<td>38</td>
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<tr>
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<td>1</td>
<td>80</td>
<td>100/70</td>
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<tr>
<td>11</td>
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<td>100/70</td>
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<td>25</td>
<td>80</td>
<td>100/70</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>80</td>
<td>100/70</td>
<td></td>
</tr>
</tbody>
</table>

If you can’t believe it, it is probably not true...

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Study Day</th>
<th>Heart Rate</th>
<th>Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>1</td>
<td>120</td>
<td>70/50</td>
</tr>
<tr>
<td>10</td>
<td>120</td>
<td>70/50</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>120</td>
<td>70/50</td>
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<tr>
<td>23</td>
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<td>9</td>
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</tr>
<tr>
<td>47</td>
<td>100</td>
<td>120/70</td>
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Disclaimer:

The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.

What This Lecture will Address/Review

- Key Activities in a Clinical Trial
  - The Process Approach
- Brief History of GCP (U.S. and international)
- Goals and Principles of GCP
- Roles and Responsibilities Under GCP
  - Investigators
  - Sponsors/Contract Research Organizations
  - Ethics Committees