Monthly IRB-Investigator Meeting

Compliance at CUMC
Common Noncompliance Findings and How to Avoid Them

March 25, 2014

Brenda Ruotolo
Interim Executive Director, IRB
Objectives

• Overview of Columbia’s Compliance Oversight Program
• Process for Handling Allegations of Noncompliance
• Definition of Serious Noncompliance
• Reporting to the IRB, Federal Agencies
• Common Findings
• Corrective Action Plans
Compliance Oversight Program (COT)

COT activities:
- reporting as required by 45 CFR 46.103(b) and 21 CFR 56.108(b)] (serious or continuing noncompliance; UP requiring change; suspension or termination of IRB approval);
- investigation of allegations of noncompliance (research or IRB);
- routine (e.g., quality or not-for-cause audits);
- review of subject complaints reported to the IRB;
- review of results of external monitoring activities and maintenance of repository of reports (e.g., FDA, NCI oncology-group studies, etc.);
- guidance/consultation for FDA audits;
- consultation for corrective action plans.
Comply with what?

• Federal Regulations
  - HHS Regulations (45 CFR 46)
  - FDA Regulations (21 CFR 50, 56, 312, 600, 812)
  - Privacy Rule (Health Insurance Portability and Accountability Act of 1996)

• NY State Law (e.g., Article 24A (2440-6); Article 7 (79-I))

• Institutional Policies

• IRB approved protocol, requirements and determinations

Columbia University Policy

All potential noncompliance with applicable statutes, policies or requirements for the protection of human subjects in research must be promptly reported to the IRB.

Concerns about possible research noncompliance may be discussed with an IRB Chair or IRB Director.

Any individual may make an allegation of noncompliance. Any such allegation shall be documented in writing and forwarded as described in the IRB Noncompliance Policy.
Serious Noncompliance

Any Noncompliance in a non-exempt study that materially increases the risks or materially compromises the rights and welfare of subjects or the integrity of the research data.

Serious noncompliance may include, but is not limited to:

• Obtaining informed consent using an invalid or outdated ICF that does not contain all of the information that might affect an individual’s willingness to participate in the research study;
• Enrollment of a subject who does not meet all eligibility criteria without obtaining prospective IRB and, if applicable, sponsor approval to be enrolled;
• Failure to perform follow up procedures required in the research protocol when the lack of follow up places the subjects at increased risk of harm;
Serious NC examples (cont.)

- Misadministration of an investigational drug or device (i.e., the drug, device or biologic, whether or not it is FDA-approved, that is the focus of a clinical investigation);
- Failure to obtain prospective IRB approval of a research study;
- Failure to obtain informed consent from subjects;
- Failure to report a serious unanticipated problem to the IRB, as defined by the CU IRB Policy on Reporting to the IRB of Unanticipated Problems Involving Risks;
- Failure to obtain prospective IRB approval of a substantive change in the conduct of the research except when the implementation of such change is required to avoid imminent harm to subjects.
Continuing Noncompliance

The occurrence of the same or similar Noncompliance after appropriate corrective action has been instituted, or the failure to institute corrective actions, taking into consideration all relevant factors, including, for example,

(a) whether the continuing Noncompliance was intentional or

(b) whether the investigator complied with the corrective action requirements and the continuing Noncompliance was not intentional.
IRB Determinations for Noncompliance Cases

- Have all necessary information?
- Level of noncompliance?
- Suspend/terminate?
- Subjects to be notified?
- Data can be used?
- Specific statement in publications about IRB approval?
- Corrective actions?
- Recommendations for sanctions?
- Monitoring?
The IRB will report noncompliance to:
- designated IRB;
- institutional officials, deans, department chairs;
- legal counsel;
- the appropriate regulatory agencies (e.g., OHRP, FDA, etc.), if the NC is serious or continuing.

Notification may also be made to sponsors.
<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Cases</strong></td>
<td>47</td>
<td>44</td>
<td>68</td>
<td>97</td>
<td>91</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>For-cause</td>
<td>30</td>
<td>22</td>
<td>34</td>
<td>52</td>
<td>75</td>
<td>50</td>
<td>36</td>
</tr>
<tr>
<td><strong>Not-for-cause</strong></td>
<td>5</td>
<td>16</td>
<td>24</td>
<td>20</td>
<td>3</td>
<td>20</td>
<td>42</td>
</tr>
<tr>
<td>Subject inquiries</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>14</td>
<td>7</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>IRB suspensions</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>4</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td><strong>Unanticipated Problem for reporting to federal agency</strong></td>
<td>8</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>8</td>
<td>2*</td>
</tr>
</tbody>
</table>

*Both determined to not meet reporting criteria*
Common Findings

Failure to obtain or maintain IRB approval
- initiation of any research related activities prior to IRB approval;
- conducting research related activities during a lapse in IRB approval.

- *Know when IRB review is required*
- *Have a plan for timely submitting renewal requests*
- *Allow time for the appropriate IRB review*
- *Provide all requested information to the IRB*
Common Findings (cont.)

“Did my IRB submission really say it would be done like that?” Approved protocol is not followed

• Over-enrollment beyond FDA or IRB-approved sample size

• Failure to satisfy inclusion/exclusion criteria

• Failure to protect confidentiality/privacy of study data in accordance with the protocol;

• Study procedures conducted incorrectly (e.g., duration, timing, dose)

• Recording procedures w/o IRB approval

• Data security procedures are not followed (e.g., access, storage)
Common Findings (cont.)

Not abiding by the recruitment or consent plan in the IRB-approved protocol

- Make recruitment plans clear; provide details follow the plan.
  i.e., ‘We will post fliers in the Emergency Department (flier attached) and we will call subjects who previously participated in IRB protocol # 0099-101 that agreed to be contacted for future research studies (see phone script attached).’

- Consider the consent process carefully before IRB submission
  i.e., who, when, how.
Common Findings (cont.)

Using documents (fliers, brochures, phone calls, e-mails) that are not IRB-approved

- update files and inform team when documents change
- altering even a number on a flier requires IRB review
- confirm that newly approved documents are appropriately stamped
- when in doubt call the IRB
Common Findings (cont.)

Failure to obtain legally-effective consent and/or HIPAA Authorization

*Obtaining consent is a PROCESS (IRB consent and HIPAA authorization) not just a signature.*

- Have an effective consenting process. Spend more time on subject questions now, have less problems later.

Signature issues

- *Subject signs and dates then person obtaining consent signs and dates*
  - dates need to match or an explanation must be documented
  - all signature lines have to be addressed
Common Findings (cont.)

Consent/authorization documentation issues

- HIPAA Authorization form and IRB consent form are not signed at the same time and/or the Authorization form is signed after a portion of the study is completed. (Document, if there is a valid reason.)
  
  *Before you collect any data or perform any screening, make sure the subject signs both forms.*

- Forms that were not IRB-approved are signed.
- Superceded forms were used.
- Check boxes for additional tests/samples/procedures not checked or initialed.
- Failure to file copy of signed CF in medical record when required
Common Findings (cont.)

“Documentation? What documentation?”

Missing, incomplete, or vague source or other documentation

– Promptly and accurately enter notes
– Have a standard notes page
– Document the visit dates, when consent was obtained, any questions answered, anything of interest, in chronological order
– Staff and co-investigators may change so clear documentation is critical
– Maintain complete copies of all signed documents
Source documents should be:

- Attributable
- Legible
- Contemporaneous
- Original
- Accurate
Common Findings (cont.)

Poor organization of electronic records and data

“It’s time for my continuing review and I can’t find my protocol and/or consent form - can you send it to me?”

- Keep related protocol documents together in one clearly marked folder on a secure drive.
- Include document file location (e.g., drive and folder name) in the footer of documents so you will know where to find them.
- Give the documents reasonable titles with version #’s
  - ‘AAZZ9876 CF v2 Jan 9 2013’ is informative;
  - ‘Blood study consent’ is not.
- Be sure someone else can get to documents if necessary.
- Back-up your files regularly (i.e. M-F 4:45pm, every Friday 4pm, etc.)
Common Findings (cont.)

Study records are not maintained

*Keep a log of all study-related protocol actions to facilitate preparation of future IRB submissions*

- Provide the number of subjects enrolled, completed, withdrawn, dropped out, etc.
- Account for all modifications that have been made or need approval
- Account for safety monitoring over the past year and ensure that all UPs have been reported
- Account for progress reports; if S-I study, annual update to FDA.
Common Findings (cont.)

Study protocols not carefully designed

• The IRB protocol is the exact plan you will be abiding by for the duration of the study (unless you submit an amendment). Any variation from that plan needs to be reported as a ‘deviation’ or ‘violation.’

• Study visits should be planned around safety monitoring and scientific needs for the study with consideration of appropriate study visit windows to minimize deviations.

• Create appropriate inclusion and exclusion criteria that meet the scientific needs of the study and that consider feasibility.

• Provide clear endpoints and rules for changing dosages for management of toxicity

• Carefully select the type and frequency of study procedures with consideration of feasibility

• CTSA offers study design consultation for faculty
Common Findings (cont.)

Personnel and internal communication issues

• Select qualified personnel
  – Ensure all have necessary credentials
  – Plan to periodically assess credentials
  – Restrict participation if training or other requirements not met

• Delegate but know what’s going on and where things are
  – Clear and accessible delegation of authority log

• Have regular team meetings

• Ensure that only authorized personnel are involved
Common Findings (cont.)

Insufficient resources to appropriately conduct the study
- shortcuts are taken
- documentation is not complete, clear, or maintained
- sponsor requirements are not met (for S-I studies)
- investigational products are not maintained appropriately
- and so on……..

- Plan
- Know your limitations
- Discuss with department
- Ask for help when necessary
Common Findings (cont.)

Non-CU IRB approvals or reliance agreements not in place

- Documentation of local IRB approval(s) (e.g., collaboration or subsite) missing or approval expired
- Execution of IIAs or IAA not completed or incorrectly completed

- Work closely with the IRB
- Allow additional time
- Carefully consider requirements
- Submission in Rascal is always required for tracking, even if Columbia is not the IRB of record
Common Findings

Regulatory documents are not appropriately maintained.

- See Clinical Research Handbook for guidance
- Regulatory documents may be paper or electronic
- Assess completeness of documentation after each regulatory action
Miscellaneous Findings

• Failure to obtain Sponsor and IRB approval for eligibility waivers

• Failure to report unanticipated problems promptly to the IRB

• Failure to report SAEs to the sponsor (and FDA for investigator held IND/IDE studies)

• Failure to maintain drug accountability records

• Inappropriate access to medical records
General Considerations for Corrective Action Plans

- Account for noncompliance findings
- Conduct root-cause analysis
- Develop processes that will prevent future noncompliance
- Consider ability to implement and maintain new process
- Consider burden of maintaining new process
- Assess effectiveness
Conducting Research “Right”

- Know what requires IRB review
- Obtain and maintain IRB approval
- Organize and maintain regulatory documents
- Select appropriate personnel and monitor
- Establish roles; PI always maintains overall responsibility
- Ensure solid communication within the team
- Abide by the IRB-approved protocol as currently approved
- Seek IRB approval for changes
- Report violations, and notifications of audits/inspections
- Close the study when completed
Columbia IRB Websites:

**CUMC:** [http://www.cumc.columbia.edu/dept/irb/](http://www.cumc.columbia.edu/dept/irb/)

**CU-MS:** [http://www.columbia.edu/cu/irb/](http://www.columbia.edu/cu/irb/)